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N-Acylation of 4-alkylidene-β-lactams: unexpected results

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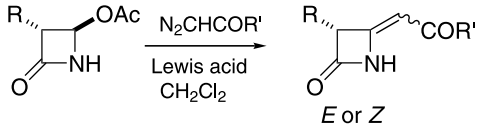
Abstract—This paper describes the different reactivity of *E*- and *Z*-4-alkylidene-β-lactams in acylation reactions under basic conditions. The *E* isomer is readily acylated, whereas the *Z* reacted sluggishly rearranging to the corresponding oxazin-6-one. The *N*-acylation of *Z* isomers was successfully obtained with oxalyl- or malonyl chlorides in benzene at reflux.

The chemistry of β-lactams has been offering a continuous occasion to get a lot of new synthetic methods and transformations. β-Lactams, in fact, have gained substantial interest in the scientific community not only due to their meaningful biological activity, but also as reactive intermediates and as starting materials in a wide range of syntheses.[1]

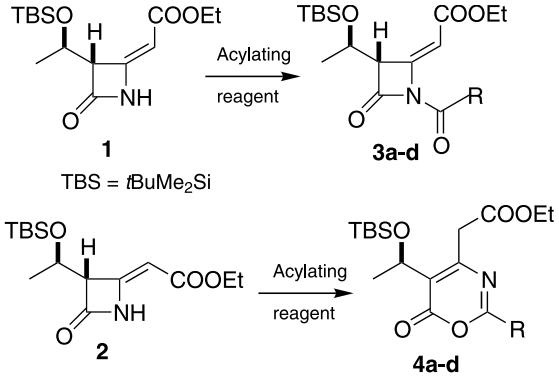
In the progress of a study on new β-lactams as inhibitors of serine-dependent enzymes and matrix metalloproteases, we found active over human leukocyte elastase and gelatinases MMPs some 4-alkylidene-β-lactam derivatives.[2] Their synthesis was accomplished starting from 4-acetoxy-azetidinones and acyldiazo compounds with a Lewis acid promotion (Scheme 1). By this method we obtained different amounts of *E*- and/or *Z*-4-alkylideneazetidinones depending on the Lewis acid and on the diazocompound.

In a tentative acylation reaction of the β-lactam nitrogen atom, we found a completely different behaviour of *E* and Z isomers. *N*-Acetylation of the *E* isomer **1** with acetic anhydride and solid K_2CO_3 in acetone was rapid, giving product **3a**, whereas, unexpectedly, the *Z* isomer **2** reacted sluggishly rearranging to the corresponding oxazin-6-one **4a** (Scheme 2, Table 1). Compound **2**, in fact, requires at least 2 equiv. of K_2CO_3 for satisfactory yields of oxazin-6-ones, with 1 equiv. of the base only traces of **4a**, together with unreacted **2**, was detected in the reaction mixture. This different behaviour persisted with some other acylating agents such as CbzCl or benzylisocyanate.

In a typical procedure compound **1** or **2** (0.31 g, 1 mmol) and benzylchloroformate (0.15 mL, 1 mmol), were dissolved in anhydrous acetone (10 mL); K_2CO_3 (0.14 g, 1 mmol for **1** and 2 mmol for **2**) was added and the reaction mixture was stirred for 1 h for **1** and overnight for **2**[3]. Then K_2CO_3 was filtered off, the solvent was removed and the crude oily residue was immediately purified by flash chromatography. Aqueous work-up of the crude must be avoided because of product decomposition. The structures of **3a–d** and **4a–d** were established by IR, ^1H and ^{13}C



Scheme 1.



Scheme 2.

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Table 1. *E*-*N*-Acyl-β-lactams (**3**) and oxazin-6-ones (**4**) starting from 4-alkylidene-azetidinones according to Scheme 2

Entry	Substrate	Acylating reagents and conditions	R	Product	Yield[a] (%)
1	**1**	Ac_2O, K_2CO_3 acetone	CH_3	**3a**	80
2	**1**	Benzylchloroformate, K_2CO_3 acetone	OCH_2Ph	**3b**	69
3	**1**	Benzylisocyanate, K_2CO_3 acetone	$NHCH_2Ph$	**3c**	60
4	**1**	Benzoyl chloride, K_2CO_3 acetone	Ph	**3d**	63
5	**2**	Ac_2O, K_2CO_3 acetone	CH_3	**4a**	77
6	**2**	Benzylchloroformate, K_2CO_3 acetone	OCH_2Ph	**4b**	54
7	**2**	Benzylisocyanate, K_2CO_3 acetone	$NHCH_2Ph$	**4c**	60
8	**2**	Benzoyl chloride, K_2CO_3 acetone	Ph	**4d**	47

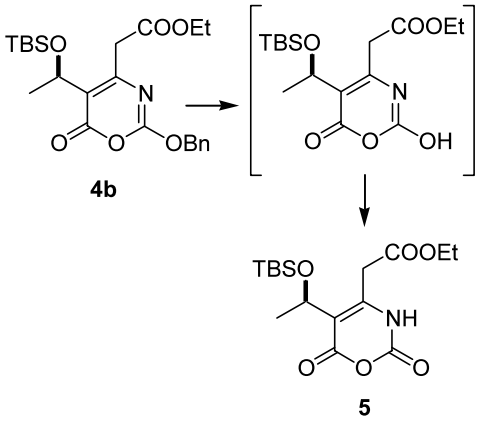
[a] Yields after flash chromatography.

NMR.[4] Quite characteristic is the IR absorption of the 4-alkylidene-β-lactam carbonyl group at 1818–1853 cm^{-1} while in oxazin-6-ones there is a shift at 1739–1752 cm^{-1}.

O-Deprotection of **4b** with H_2 and Pd on carbon in THF gave the oxazin-2,6-dione **5**, a stable, crystalline compound whose structure was definitively confirmed by X-ray diffraction analysis (Scheme 3, Fig. 1).[5]

Rearrangements of β-lactams into oxazines or of oxazines into β-lactams have already been observed.[6] Alajarin et al.[7] investigated the mechanism for the oxazine formation from *N*-acyl-4-acetoxy-β-lactams throughout the formation of a highly unstable *N*-acyl azetone that rearranges into the six membered ring. Under our reaction conditions (K_2CO_3, acetone) we suppose an initial formation of *N*-acyl-*Z*-4-alkylideneazetidinone (Scheme 4, intermediate **A**) followed by a base-induced endocyclic isomerization of the C=C bond giving the corresponding *N*-acyl azetone (**B**).[8] This intermediate should quickly rearrange into the oxazin-6-one **D** via a ketene-acylimine intermediate **C**.

We have indirect evidence that the allylic isomerization follows the acylation of the β-lactam nitrogen atom, in fact, a longstanding treatment of *E*-4-alkylidene-β-lactam **1** with K_2CO_3/acetone without any acylating agent leads to isomerization into the Z isomer **2**, which results stable in these reaction conditions. No traces of azetone or any other decomposition products have been



Scheme 3.

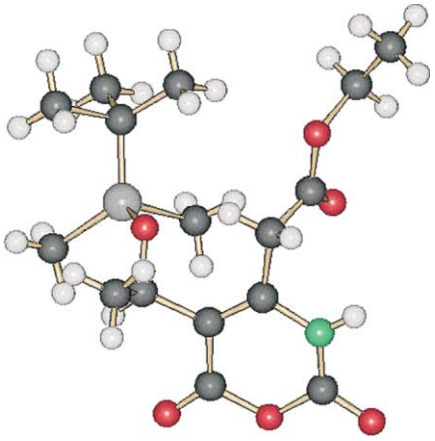


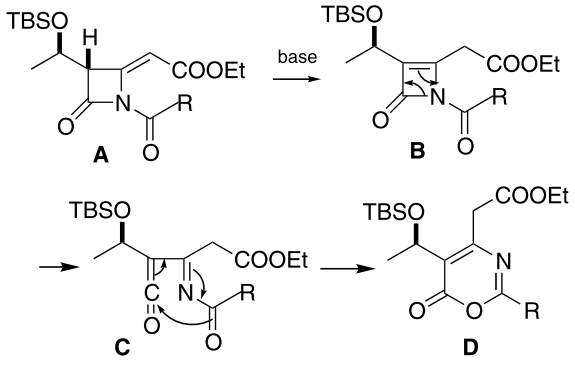
Figure 1. Crystal data for **5**: $C_{16}H_{27}NO_6Si$, $M=357.48$, orthorhombic, $P2_12_12_1$, $a=7.306(5)$, $b=16.415(5)$, $c=16.766(5)$ Å, $V=2010.7(2)$ Å^3, $Z=4$, $T=293(2)$°C, μ(Mo-Kα)$=0.144$ mm^{-1}, 15557 reflections measured, 2919 unique ($R_{int}=0.0892$), $R_1=0.0784$, $wR_2=0.2133$.

detected in the reaction mixture.[9] Moreover, treatment of *E* isomer of *N*-acetyl derivative (**3a**) with an excess of K_2CO_3 at room temperature gave the corresponding oxazin-6-one **4a**.

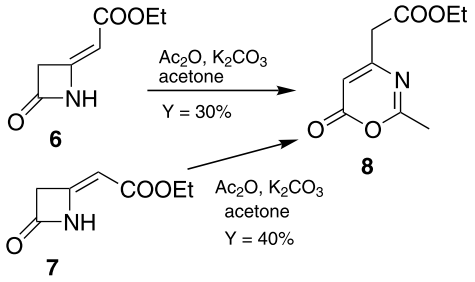
The endocyclic double bond rearrangement under basic conditions, depends on the *E* or *Z* geometry of the C=C bond and on the C-3 side chain. For instance, treatment of the two *E*- and *Z*-4-alkylidene-β-lactams unsubstituted on the C-3 position (azetidinones **6** and **7**, Scheme 5) with acetic anhydride in acetone with solid K_2CO_3 resulted in the formation of the sole oxazin-6-one **8**.

A careful exploration of the reaction conditions (starting β-lactam, acylating agent and solvent), allowed us to successfully obtain *Z* isomers of *N*-acyl-4-alkylidene-azetidinones (Table 2). Critical resulted the use of mono chloro oxalyl esters or ethyl malonyl chloride as acylating agents in benzene at reflux.[10] The reaction of β-lactam **9** and mono chloro oxalyl esters gave good yields, and the products can be directly recovered by evaporation, under reduced pressure, of volatile components from the crude (Scheme 6 and Table 2).

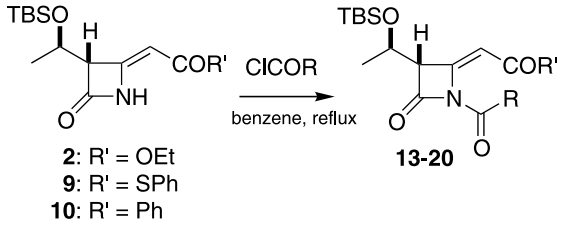
In summary, we have developed a new route to *N*-acyl-4-alkylidene-azetidin-2-ones *Z* and *E*. The reaction con-



Scheme 4.



Scheme 5.



Scheme 6.

ditions depend on the *Z* or *E* isomer. Under basic conditions (K_2CO_3, acetone) the *E* isomer is readily acylated whereas *Z* isomer rearranges into oxazines. *N*-Acylation of *Z* isomers was successfully achieved with oxalyl or malonyl monoester chlorides in benzene at reflux.

Biological activity of these new *N*-acyl-4-alkylidene azetidin-2-ones is actively under investigation.

Acknowledgements

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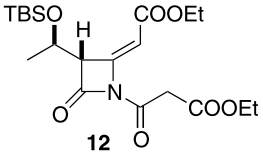
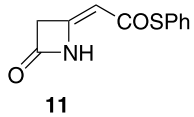
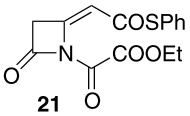
Table 2. *N*-Acyl-β-lactams (**12**–**21**) starting from 4-alkylidene-azetidinones according to Scheme 6

Entry	Substrate	R′	R	Product	Yield[a] (%)
1	**1**	OEt	CH_2COOEt	 **12**	30
2	**2**	OEt	CH_2COOEt	**13**	29[b]
3	**2**	OEt	COOEt	–	–
4	**9**	SPh	COOEt	**14**	85
5	**9**	SPh	$COOpNO_2Bn$	**15**	80
6	**9**	SPh	$COOtBu$	**16**	83
7	**9**	SPh	$COOCH_2CH{=}CH_2$	**17**	80
8	**9**	SPh	COOBn	**18**	89
9	**10**	Ph	COOEt	**19**	90
10	**10**	Ph	$COOCH_2CH_2SiMe_3$	**20**	90
11	 **11**	SPh	COOEt	 **21**	50

[a] Conversion determined by ^1H NMR analyses of the crude.
[b] A 20% of the corresponding oxazin-6-one was detected in the crude by NMR analyses.

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3. The sequence in reagent addition is quite important. In fact addition of the acylating agent to the acetone suspension of **1** and K_2CO_3 resulted in the formation of the sole oxazin-6-one **4a**, because the acylation follows the preliminary basic isomerization of **1** in **2**.
4. Selected data **3a**: $[\alpha]_D^{25}=-180$ (*c* 0.13, $CHCl_3$). IR (film): 2959, 1832, 1726, 1660, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ −0.07 (s, 3H), 0.03 (s, 3H), 0.80 (s, 9H), 1.30 (t, $J=6.8$ Hz, 3H), 1.40 (d, $J=6.4$ Hz, 3H), 2.42 (s, 3H), 4.05 (dd, $J=1.4$ Hz, $J=1.6$ Hz, 1H), 4.20 (q, $J=6.8$ Hz, 2H), 4.73 (dq, $J=6.4$ Hz, $J=1.6$ Hz, 1H), 6.52 (d, $J=1.4$ Hz, 1H).^{13}C NMR ($CDCl_3$, 50.29 MHz): δ −5.5, −4.4, 14.4, 17.7, 22.0, 24.1, 25.5, 60.3, 65.0, 65.6, 99.6, 150.3, 165.7, 166.5, 166.7. **4a**: $[\alpha]_D^{25}=+24$ (*c* 0.5, $CHCl_3$). IR (film): 1739, 1639, 1586, 1076, 943 cm^{-1}—^1H NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.28 (t, 3H, $J=7.2$ Hz), 1.39 (d, 3H, $J=6.6$ Hz), 2.37 (s, 3H), 3.83 (d, 1H, $C=CCH_AH_BCO_2$, $J_{AB}=16.0$ Hz), 4.10 (d, 1H, $C=CCH_AH_BCO_2$, $J_{AB}=16.0$ Hz), 4.19 (dq, 2H, $CH_3CH_2CO_2$, $J=7.2$ Hz, $J=1.2$ Hz), 5.20 (q, 1H, CH_3CHOSi, $J=6.3$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.2, −5.1, 14.1, 18.0, 21.2, 23.7, 25.8, 39.6, 61.0, 63.9, 123.4, 156.5, 159.6, 163.9, 169.2. **4c**: IR (CH_2Cl_2): 1739, 1627, 1567, 1301, 1255, 911, 738 cm^{-1}—^1H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.26 (t, 3H, $J=7.4$ Hz), 1.38 (d, 3H, $J=6.6$ Hz), 3.83 (d, 1H, $C=CCH_AH_BCO_2$, $J_{AB}=16.0$ Hz), 4.09 (d, 1H, $C=CCH_AH_BCO_2$, $J_{AB}=16.0$ Hz), 4.18 (dq, 2H, $CH_3CH_2CO_2$, $J=7.2$ Hz, $J=2.6$ Hz), 5.15 (q, 1H, CH_3CHOSi, $J=6.6$ Hz), 5.33 (d, 1H, OCH_AH_BPh, $J_{AB}=12.0$ Hz), 5.39 (d, 1H, OCH_AH_BPh, $J_{AB}=12.0$ Hz), 7.30 (m, 5H)—^{13}C NMR (50 MHz, $CDCl_3$): δ −5.2, −5.0, 14.1, 18.0, 24.0, 25.8, 40.2, 61.0, 64.1, 71.4, 117.9, 128.2, 128.5, 128.7, 134.0, 156.9, 159.2, 159.7, 169.0. **5**: $[\alpha]_D^{25}=+28$ (*c* 0.5, $CHCl_3$)—IR (Nujol): 3250, 3204, 1765, 1739, 1719, 1646 cm^{-1}—^1H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 1.33 (t, 3H, $J=7.2$ Hz), 1.36 (d, 3H, $J=6.6$ Hz), 1.62 [bs, 1H, N***H***), 3.88 (d, 1H, $C=CCH_AH_BCO_2$, $J_{AB}=17.2$ Hz), 4.08 (d, 1H, $C=CCH_AH_BCO_2$, $J_{AB}=17.2$ Hz), 4.26 (q, 2H, $J=7.2$ Hz), 5.10 (q, 1H, CH_3CHOSi, $J=6.6$ Hz)—^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.2, −5.1, 14.0, 18.0, 24.3, 25.8, 33.4, 62.5, 64.3, 111.6, 147.4, 159.1, 159.2, 168.5. **8**: IR (CH_2Cl_2): 1762, 1746, 1635, 1581 cm^{-1}—^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, 3H, $J=7.4$ Hz), 2.40 (s, 3H, $CH_3C=N$), 3.46 (s, 2H, CH_2CO_2Et), 4.24 (q, 2H, $CH_3CH_2CO_2$, $J=7.4$ Hz), 6.12 (s, 1H, CH=C)—^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 21.6, 29.7, 42.2, 61.6, 107.7, 158.8, 160.7, 167.2, 168.1. **19**: IR (CH_2Cl_2): 1853, 1757, 1717, 1679, 1618 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.12 (s, 3H), 0.17 (s, 3H), 0.91 (s, 9H), 1.23 (d, 3H, $J=6.3$ Hz), 1.40 (t, 3H, $J=7.0$ Hz), 4.44 (q, 2H, $CH_3CH_2CO_2$, $J=7.0$ Hz), 4.52 (dd, 1H, CH_3CHOSi, $J=1.4$ Hz, $J=4.4$ Hz), 4.76 (dq, 1H, $J=4.4$ Hz, $J=6.3$ Hz), 7.65 (d, 1H, CH=C, $J=1.4$ Hz), 7.53 (m, 3H), 7.98 (m, 2H)—^{13}C NMR (50 MHz, $CDCl_3$): δ −5.2, −4.8, 13.7, 17.8, 20.4, 25.5, 63.4, 64.9, 65.5, 66.5, 105.2, 128.2, 128.3, 128.6, 133.3, 137.6, 147.7, 163.8, 189.2.
5. Crystallographic data (excluding structure factors) for compound **5** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 211163. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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9. Compound **2** results thermodynamically more stable than **1** because of the intramolecular hydrogen bond between the NH and the COOEt in the side chain, see for instance Ref. 2.
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