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Synthesis of novel 4-(1-ethoxycarbonyl-methylidene)-azetidin-2-ones via a Lewis acid-catalyzed reaction of ethyl diazoacetate

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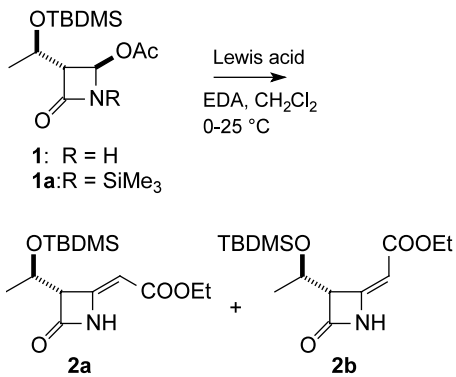
Abstract—Treatment of (3*R*,4*R*,1′*R*)-3-[1-(*t*-butyldimethylsilyloxy)ethyl]-4-acetoxy-azetidin-2-one with ethyl diazoacetate in the presence of a Lewis acid such as $TiCl_4$, TiF_4, $AlCl_3$ or $SnCl_4$ affords the novel (3*S*,1′*R*)-3-[1-(*t*-butyldimethylsilyloxy)ethyl]-4(1-ethoxycarbonyl-methylidene)-azetidin-2-one as an *E* and/or *Z* isomer. © 2002 Published by Elsevier Science Ltd.

The unique chemotherapeutic properties of β-lactam antibiotics continue to attract the attention of the chemical community. The β-lactam nucleus is considered to be a general lead-structure for the design and synthesis not only of new antibacterial products, but also of new inhibitors of enzymes containing a serine nucleophile in their active site, like β-lactamases,[1] human leukocyte elastase,[2] cholesterol absorption inhibitors[3] and human cytomegalovirus protease.[4] Strategies for the stereoselective synthesis of carbapenems, penems, monobactams and trinems usually rely first on the construction of a monocyclic azetidin-2-one bearing the appropriate functionalities on C-3 and C-4. In this regard the (3*R*,4*R*,1′*R*)-3-[1-(*t*-butyldimethylsilyloxy)ethyl]-4-acetoxy-azetidin-2-one (**1**) has been recognized as a versatile building block.[5] Recently, we reported a facile stereocontrolled synthesis of **1** starting from methyl (*R*)-3-hydroxybutyrate and hexahydrotriazine.[6] As part of our ongoing studies in the area of β-lactams,[7] some years ago we reported the synthesis of 4-alkylidene-azetidin-2-ones starting from ester–enolate and ketenimine.[8] We report here a novel reaction of **1** with ethyl diazoacetate in the presence of a Lewis acid to directly give the corresponding 4-methylidene derivative, and describe the synthesis and characterization of the novel (3*S*,1′*R*)-3-[1-(*t*-butyldimethylsilyloxy)ethyl]-4(1-ethoxycarbonyl-methylidene)-azetidin-2-one (**2**) (Scheme 1).

We initiated our study by reacting compound **1** and ethyl diazoacetate (EDA)[9] in the presence of a catalytic amount of $TiCl_4$ in CH_2Cl_2, but we obtained only traces of the 4-alkylidene compound. Next, we investigated the coupling of **1** and its *N*-trimethylsilyl derivative (**1a**) with different amounts of EDA and different Lewis acids. The results are summarized in Table 1. Critical to the success of the reaction was a stoichiometric amount of $TiCl_4$, which was associated with a requirement for in situ protection of the β-lactam nitrogen atom (Table 1, entry 6). Ethyl diazoacetate (4 equiv.) together with $TiCl_4$ (1 equiv.) improved the reaction yield from 60 to 91% (entry 7). We observed that without *N*-$SiMe_3$ protection, the yield was reduced by the formation of side and degradation products.

In a typical procedure, **1** (1 mmol) was treated with Et_3N (1.3 mmol) and Me_3SiCl (1.1 mmol) in CH_2Cl_2 (5



Scheme 1.

Keywords: beta-lactams; diazocompounds; Lewis acids; azetidinone; ethyldiazoacetate.

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Table 1. Reaction of 4-acetoxy derivatives **1** and **1a** with ethyldiazoacetate (EDA) and different Lewis acids

Entry	R	Equiv. of EDA	Lewis acid (equiv.)	Yield (%)[a]	**2a** (%)	**2b** (%)
1	H	1	–	–	–	–
2	H	1	$TiCl_4$ (0.1)	Traces	Traces	–
3	H	1	$TiCl_4$ (1)	23	>99	Not detected
4	H	4	$TiCl_4$ (1)	77	>99	Not detected
5	H	4	Me_3SiCl (2)/$TiCl_4$ (0.1)	49	>99	Not detected
6	$SiMe_3$	1	$TiCl_4$ (1)	60	85	15
7	$SiMe_3$	4	$TiCl_4$ (1)	91	80	20
8	$SiMe_3$	4	Me_3SiCl (2)/$TiCl_4$ (0.1)	81	60	40
9	$SiMe_3$	4	TiF_4 (1)	72	58	42
10	$SiMe_3$	4	$SnCl_4$ (1)	35	>99	Not detected
11	H	4	$SnCl_4$ (1)	58	>99	Not detected
12	$SiMe_3$	4	$AlCl_3$ (1)	73	53	47
13	H	4	$AlCl_3$ (1)	45	50	50
14	$SiMe_3$	4	Et_2AlCl (1)	59	50	50
15	$SiMe_3$	1	Me_3SiCl (1)	–	–	–
16	$SiMe_3$	4	$BF_3{\cdot}Et_2O$ (1)	18	Not detected	>99
17	$SiMe_3$	4	$ZnCl_2$ (1)	16	>99	Not detected

[a] Isolated yields after flash chromatography.

mL) at room temperature. After 1 h, $TiCl_4$ (1 mmol) was added in one portion at 0°C followed by dropwise slowly addition of a solution of ethyldiazoacetate (4 mmol) in CH_2Cl_2 (2 mL). The resulting brown solution was stirred for 3 h. Products **2a** and **2b** were obtained in an 8/2 ratio with a combined yield of 91% after silica gel chromatography. Among the Lewis acids tested, $ZnCl_2$ and $BF_3{\cdot}OEt_2$ promoted the reaction with excellent complementary stereoselection, but the yields were not satisfactory (entries 16 and 17). TiF_4, $AlCl_3$ and Et_2AlCl were good catalysts for this reaction, but they furnished almost equimolar **2a**/**2b** mixtures (entries 9, 12, 13, 14). $SnCl_4$ catalyzed well the addition of EDA to **1** and **1a** with the formation of *Z*-**2a** as the sole isomer (entries 10 and 11). Me_3SiCl did not promote the reaction (entry 15), but the combination of 2 equiv. of TMSCl and 10% of $TiCl_4$ gave a catalytic variant of the reaction (entries 5 and 8) with complete stereoselection for **2a** starting from **1**. Interestingly, at least with $TiCl_4$ as a catalyst, we achieved complete stereochemical control in favor of the Z isomer with the deprotected starting material **1**, whereas the *N*-$SiMe_3$ derivative (**1a**) gave **2a**–**2b** mixtures.

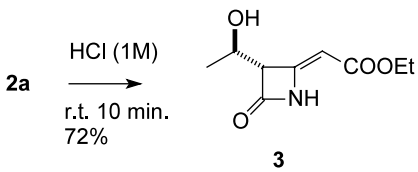
The structures of **2a** and **2b** were established by IR, ^1H and ^{13}C NMR.[10] The IR absorption of the β-lactam carbonyl group of **2a** at 1820 cm^{-1} is quite interesting, and has been previously observed in 4-alkylidene compounds obtained from enolates and chetenimines,[8] as is the more deshielded NH resonance in ^1H NMR $CDCl_3$ spectra of **2a** compared to that with **2b**.

After *O*-deprotection of **2a** with HCl in MeOH (Scheme 2), the structure of **3** was confirmed by X-ray diffraction analysis (Fig. 1).[11]

In Scheme 3 we propose a mechanism to explain the formation of products.

The reaction probably proceeds through the initial complexation of **1a** with $TiCl_4$ and the subsequent formation of an iminium ion **A**.[12] The need for a full equivalent of $TiCl_4$ in the reaction could be dictated by the need to scavenge the acetoxy group as the reaction proceeds. The iminium ion then reacts with ethyl diazoacetate to give **B** which affords 4-alkylidene derivatives after a nitrogen elimination reaction.

In conclusion, we have described the synthesis of novel 4-alkyliden-azetidin-2-ones. Further studies are currently underway to extend the present approach to the construction of a variety of optically active related products and to obtain a deeper understanding of the stereochemical control in this process, as well as to test



Scheme 2.

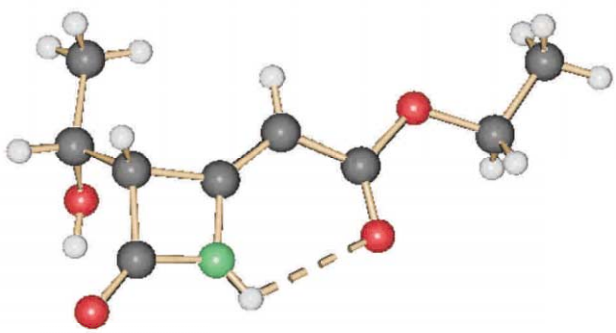
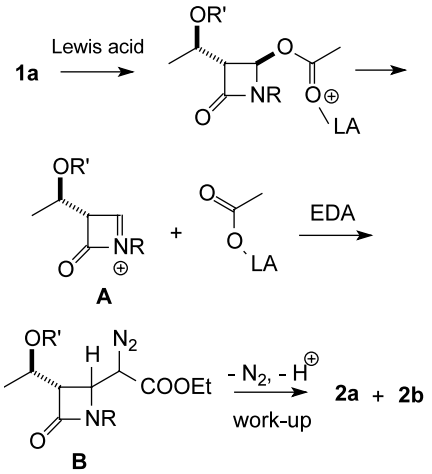


Figure 1. Crystal data for **3**: $C_9H_{13}NO_4$, $M=199.20$, monoclinic, $P2_1$, $a=5.3090(6)$, $b=9.7675(11)$, $c=19.872(2)$ Å, $\beta=91.485(3)°$, $V=1030.1(2)$ $Å^3$, $Z=4$, $T=293(2)$°C, μ(Mo-Kα)$=0.101$ mm^{-1}, 18491 reflections measured, 9161 unique ($R_{int}=0.0863$), $R_1=0.0583$, $wR_2=0.1505$.



Scheme 3.

the activity of these new compounds as protease inhibitors.

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10. **2a**: $[\alpha]_D^{25}=-41°$ ($c=0.53$, $CHCl_3$); IR (neat, cm^{-1}) 3250, 1821, 1693, 1652, 1238. MS (70 eV): m/z (%) = 298 (3) [M^+-CH_3], 268 (5), 256 (90) [M^+-tBu], 210 (100), 184 (14), 143 (44), 75 (32), 73 (29). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.06 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.87 (s, 9H, Si*t*Bu), 1.29 (t, $J=7.2$ Hz, 3H, CH_3CH_2), 1.31 (d, $J=6.3$ Hz, 3H, CH_3CHO), 3.66 (dd, $J=5.4$ Hz, $J=0.9$ Hz, 1H, CHOC*H*), 4.19 (q, $J=7.2$ Hz, 2H, CH_3CH_2), 4.25 (m, 1H, CHO), 5.21 (d, $J=0.8$ Hz, 1H, C=CH), 8.61 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.0, −4.3, 14.3, 17.9, 22.3, 25.6, 60.1, 64.7, 65.1, 90.3, 153.3, 166.7, 167.2. **2b**: $[\alpha]_D^{25}=+104.5°$ ($c=0.8$, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) 3243, 3257, 3218, 1805, 1792, 1706, 1693, 1646, 1242, 1162. MS (70 eV): m/z (%) = 298 (2) [M^+-CH_3], 268 (5), 256 (92) [M^+-tBu], 210 (20), 184 (18), 143 (11), 75 (85), 73 (100). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.11 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.91 (s, 9H, Si*t*Bu), 1.22 (d, $J=6.3$ Hz, 3H, CH_3CHO), 1.28 (t, $J=7.2$ Hz, 3H, CH_3CH_2), 4.10 (m, 1H, CHOC*H*), 4.17 (q, $J=7.2$ Hz, 2H, CH_3CH_2), 4.65 (dq, $J=6.3$ Hz, $J=3.9$ Hz, 1H, CHO), 5.31 (d, $J=0.6$ Hz, 1H, C=CH), 7.9 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.0, −4.7, 14.3, 18.0, 19.5, 25.7, 59.9, 64.6, 64.7, 92.4, 153.0, 166.3, 168.0. **3**: $[\alpha]_D^{25}=-24°$ ($c=0.61$, CH_3Cl). IR (neat, cm^{-1}) 3417, 3238, 1820, 1700, 1646, 1250, 1170, 1050. MS (70 eV): m/z (%) = 199 (4) [M^+], 184 (11) [M^+-CH_3], 166 (43), 155 (57), 138 (57), 99 (100), 68 (41). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, $J=7.2$ Hz, 3H, CH_3CH_2), 1.39 (d, $J=6.6$ Hz, 3H, CH_3CHO), 2.1 (bs, 1H, OH), 3.75 (d, $J=5.7$ Hz, 1H, CHOC*H*), 4.21 (q, H, CH_3CH_2, $J=7.2$ Hz), 4.23 (m, 1H, C*H*OH), 5.27 (d, $J=0.3$ Hz, 1H, C=CH), 8.73 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 21.5, 60.3, 64.0, 64.8, 90.9, 152.2, 166.3, 166.9.
11. Crystallographic data (excluding structure factors) for the compound **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 163737. 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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