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A New Simple Route for the Synthesis of (±)-2-Azetidinones Starting from β-Enaminoketoesters

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Abstract

β-Enaminoketoesters, obtained by metal-catalyzed reaction between alkyl acetoacetates and alkyl cyanoformates, are useful starting materials for rapid access to β-acetyl-dehydroaspartic acid derivatives which could be transformed into (±)-2-azetidinones bearing a 1-hydroxy-ethyl substituent through suitable reductive processes.

Keywords: 2-Azetidinones, β-enaminoketoesters

The 2-azetidinone ring system is the common structural feature of a number of broad spectrum β-lactam antibiotics, including penicillins, cephalosporins, carbapenems, nocardicins and monobactams, which have been widely used as chemotherapeutic agents to treat bacterial infections and microbial diseases.[1]

The pharmacological importance of these antibiotics has triggered the widespread interest of synthetic chemists in the development of new methodologies for the construction of suitably substituted 2-azetidinone ring systems.

The most usual methodologies for the construction of 2-azetidinone ring systems are generally classified as i) [2+2] cycloadditions, ii) carbene insertion reactions, and iii) cyclisation reactions of β-aminoacids and esters.[2]

Our interest in β-lactams stems from our work on metal-catalysed reactions of β-dicarbonyl compounds with nitriles.[3] In particular, it has been recently demonstrated that the metal-catalyzed reaction of alkyl acetoacetates with alkyl cyanoformates is a very attractive method for new carbon-carbon bond formation, allowing us to obtain a series of polyfunctionalized compounds having the general structure of β-enaminoketoesters,[4] which have been used for the synthesis of selected heterocycles.[5]

We next turned our attention to the easily available compounds **1a,b** which could be regarded as β-acetyl-dehydroaspartic acid derivatives. We anticipated that these α-alkoxycarbonyl β-enaminoketoesters, apart from being useful precursors for the synthesis of unusual *alpha*- and *beta*-amino acids, possess the correct carbon framework for the synthesis of 2-azetidinones bearing a 1-hydroxyethyl substituent, a structural feature common to several important natural compounds such as thienamycin and related stuctures.[1]

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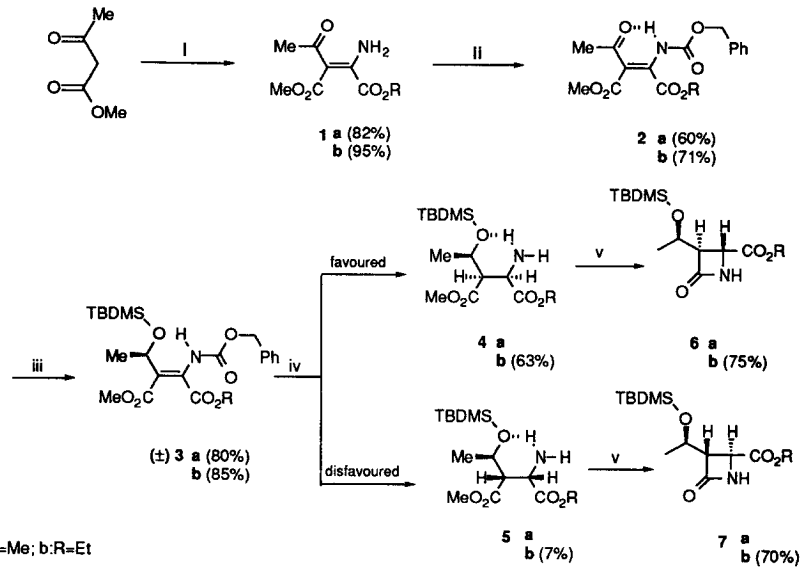
In this comunication we report the transformation of the β-enamino ketoesters **1a,b** (Scheme 1), conveniently prepared in high yield by reaction of methyl acetoacetate with methyl or ethyl cyanoformates in the presence of 2mol % $[Zn(acac)_2]$,[4a] into the 2-azetidinones **6** and **7** through two reductive operations involving the carbonyl group and the double bond of the enaminoester moiety. To this end, introduction of an electron-withdrawing group on nitrogen was required to overcome the problems associated with the reluctance of the enaminone moiety to undergo reduction under mild conditions. Thus, compounds **1a,b** were transformed into the *N*-protected enamino ketoesters **2a,b** in good yield by reaction with benzyl chloroformate in the presence of sodium hydride.



I: NC-COOR, $[Zn(acac)_2]$ 2 mol%, CH_2Cl_2, rt,1.5h; II: $ClCO_2CH_2Ph$, NaH, THF, 0°C, 1 h; III: 1. $NaBH_4$, MeOH, 0°C, 10 min; 2. TBDMSCl, imidazole, rt, 3h; Iv: H_2, Ni Raney, EtOH, rt, 8h; v: 1. TMSCl, Et_3N, CH_2Cl_2, rt; 2. t-BuMgCl.

Scheme 1

The reduction of the ketone with $NaBH_4$ in methanol followed by protection of the derived secondary hydroxyl group by treatment with *tert*-butyl dimethylsilyl chloride in the presence of imidazole gave compounds **3a,b** in good yield.

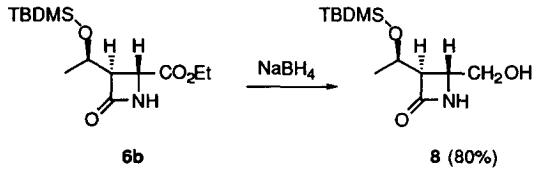
The reduction of C-C double bond of compounds **3a,b** was achieved under very mild conditions by treatment with hydrogen in the presence of Raney Nickel W-2 as the catalyst in ethanol at room temperature for 8 h, giving rise to a 9:1 mixture of the aminoesters **4** and **5** in 65-70% yield.

Attempts to separate the methyl ester derivatives **4a** and **5a** were unsuccessful while the corresponding ethyl esters **4b** and **5b** were easily separated by flash chromatography.

Treatment of the mixture of isomers **4a** and **5a** with trimethylsilyl chloride in the presence of

Et_3N, followed by addition of *tert*-butyl magnesium chloride, afforded a 9:1 mixture of the azetidinones **6a** and **7a** in 65% yield, the main diastereomer **6a** being easily separated by flash-chromatography. Under the same experimental conditions the separated amino esters **4b** and **5b** were converted in the two azetidinones **6b**[6] and **7b** respectively in 70-75% yields.

The ^{1}H-NMR spectrum of all the compounds obtained agrees with an azetidinone structure in which the two hydrogens linked to C-3 and C-4 carbon atoms are in a *trans* configuration, but the spectroscopic data was not sufficient to assign the relative configuration of the newly created stereocenters. However, assignment of the correct configuration became possible through X-ray analysis[7] of the crystalline primary alcohol **8** derived from reduction of **6b** with $NaBH_4$ (Scheme 2).



6b **8 (80%)**

Scheme 2

Based on the structure of **8**, we could assign the structures reported in the scheme 1 to compounds **6** and **4** (these compounds are obviously mixture of enantiomers but only one of them is drawn).

The diastereoselectivity observed in these reactions may be accounted for by the cyclic structure of the intermediate **3**, which is particularly stable because of the strong hydrogen bond between the NH and the oxygen atom linked to silicon. Thus, the reduction of this intermediate can occur from the less hindered side of the molecule (favoured pathway) giving rise to the amino esters **4**, in which the hydrogens linked to C-2, C-3 and C-4 carbon atoms are on the same side of the plane of the molecule. The cyclization of **4** to **6** requires a rotation of the C2-C3 single bond eventually producing the *trans* azetidinone **6**. The formation of the minor products **5** could be explained by assuming that the hydrogenation of **3** occurs from the more hindered side of the molecule (disfavoured pathway) leading to amino esters **5**. Also in this case the cyclisation to azetidinone **7** occurs after a rotation around the C2-C3 single bond giving the diasteromeric azetidinone **7**, whose *trans* configuration was confirmed by its ^{1}H-NMR spectra.

In conclusion, we have demonstrated that the easily available compounds **1** can be conveniently utilized as building blocks for a simple synthesis of azetidinones **6**, which can be obtained in good yield and high diastereoselectivity, so opening a simple route to the synthesis of these important heterocycles. We are actively studying the reduction of the achiral starting materials with chiral reducing agents in order to establish enantioselectively the three asymmetric centers generated in the reductive steps involved in the sequence.

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References and notes

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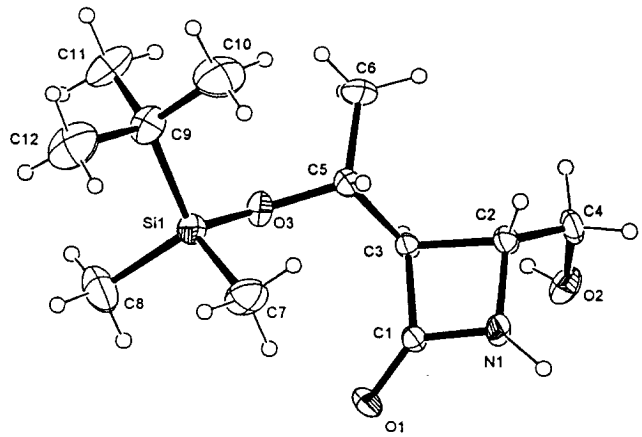
6 Spectral data of compound **6b**: ^{1}H-NMR ($CDCl_3$) δ: 0.07 (s, 3H, Me-Si), 0.09 (s, 3H, Me-Si), 0.89 (s, 9H, *t*-Bu), 1.20-1.35 (m, 6H, CH_3-CH_2 and CH_3-CH), 3.33 (br, 1H, *CH*-CO), 4.06 (d, J=2.56 Hz, 1H, *CH*-NH), 4.12-4.24 (m, 3H, OCH_2 and *CH*-CH_3), 6.64 (br, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: -4.08 (q, J=118 Hz), -4.28 (q, J=118 Hz), 14.10 (q, J=126 Hz), 17.95 (s), 20.62 (q, J=126 Hz), 25.67 (q, J=124 Hz), 50.03 (d, J=154 Hz), 61.52 (t, J=147 Hz), 63.85 (d, J=139 Hz), 64.93 (d, J=141 Hz), 167.46 (s, COO), 171.53 (s, COO).
7 **Figure**. An ORTEP view of one of the enantiomers of compound **8** displaying the thermal ellipsoids at 30% probability.



Crystal data: $C_{12}H_{25}NO_3Si$; monoclinic, space group $P2_1/a$; a = 12.852(4), b = 7.519(2), c = 16.854(4) Å, β = 108.99(2)°, V = 1540.0(7) Å^3, Z = 4, D_C = 1.12 g cm^{-3}. Intensity data collected with θ ≤ 27 ° using Mo Kα radiation (0.71073 Å) on an Enraf-Nonius CAD4 diffractometer; T = 295 K, 3310 independent reflections measured; 1426 reflections observed [I ≥ 3σ(I)]; solution by direct methods; full matrix least-squares refinement using SHELXL-97 (Sheldrick, G. M. SHELXl-97. Program for the Refinement for Crystal Structures. University of Göttingen, Germany, 1997); non-hydrogens anisotropic, methyl hydrogens atoms included at calculated positions and the remaining hydrogens refined isotropically. An ORTEP view of the molecule (Johnson, C. K., ORTEPII, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976) is shown in Figure. The molecules in the crystal are connected by two hydrogen bonds: O2-H20---O1 [O2-H20 = 0.95(7), O2---O1(3/2-x, y-1/2, 1-z) = 2.693(7) Å, O2-H20---O1 = 175(6)°] and N1-H1---O2 [N1-H1 = 0.88(5), N1---O2 (2-x, -y, 1-z) = 2.844(7) Å, N1-H1---O2 = 156(5)°]. Atomic coordinates, thermal parameters, bond lengths and angles are available from the Cambridge Crystallographic Data Centre.