Thermally Induced Isomerization of *cis*-1,3,4-Trisubstituted 2-Azetidinones

Benito Alcaide,* Pedro Almendros, Nati R. Salgado, and Alberto Rodríguez-Vicente

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

alcaideb@eucmax.sim.ucm.es

Received February 18, 2000

The importance and structural diversity of biologically active β-lactam antibiotics, the most widely employed family of antimicrobial agents to date accounting for 50% of the world's total antibiotic market, led to the development of efficient approaches for the construction of appropriately substituted 2-azetidinones with attendent control of functional groups and stereochemistry.[1] The minimun structural features believed to be essential for antimicrobial activity in the β-lactams antibiotics have undergone considerable revision, since in recent years several natural monocyclic β-lactams were shown to exhibit high antibacterial activity, now appearing that the minimum requirement for biological activity is a suitably substituted monocyclic 2-azetidinone ring.[2] Antielastase activity of 1,3,4-trisubstituted and 3,4-disubstituted 2-azetidinones has been determined against enzymes, for example, human leucocyte elastase.[3] Furthermore, the recent discoveries of some trans-3-substituted 4-aryl-β-lactams as new potent cholesterol absorption inhibitors[4] and human cytomegalovirus protease inhibitors[5] justify a renewed interest in these compounds. On the other hand, monocyclic β-lactams frequently serve as precursors for the synthesis of polycyclic β-lactam antibiotics, and they are also versatile intermediates in organic synthesis.[6] Among the most often employed methods (the hydroxamate cyclization,[7] the metalloester enolate-imine condensation,[8] the chromium carbene-imine reaction,[9] and the isocyanate−alkene cycloaddition[10]) for the synthesis of monocyclic 2-azetidinones, the [2 + 2] cycloaddition of ketenes with imines, known as the Staudinger reaction, probably is the most important and direct approach.[11] However, regarding the stereochemical outcome of the reported routes a very strong preference for *cis*-β-lactam, kinetic control product, formation is observed.[12] Previous work on isomerization of *cis*-β-lactams requires as starting materials 2-azetidinones bearing acid- or base-sensitive moieties (e.g., aldehyde, ketone, ester, amine, amide) at the position susceptible for epimerization.[13] In our ongoing project directed toward the stereoselective synthesis and applications of chiral functionalized 2-azetidinones,[14] we required an easy access to *trans*-β-lactams, having reported recently a base-promoted regiospecific C4-epimerization of *cis*-4-formyl-β-lactams.[15] Within this context and as an extension of our previous studies on the isomerization from *cis*- to *trans*-β-lactams, we wish to report here a different, hitherto unknown, strategy to access to *trans*-2-azetidinones.[16] Namely, a thermally induced stereoselective rearrangement of *cis*-1,3,4-trisubstituted β-lactams to

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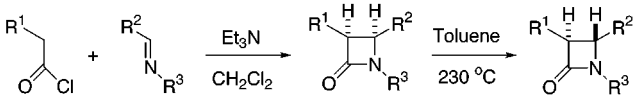
10.1021/jo000229x CCC: $19.00
Published on Web 06/13/2000

Table 1. Thermally Induced Isomerization of *cis*-*β*-Lactams 1 to *trans*-*β*-Lactams 2



1 2

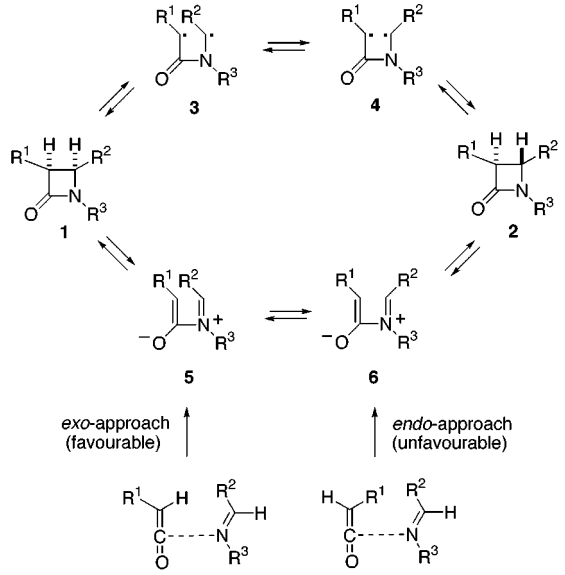
entry	R^1	R^2	R^3	*cis*-*β*-lactam	yield[a] (%)	*trans*-*β*-lactam	yield[a] (%)
1	CH_3O	3-furyl	3-butenyl	*cis*-**1a**	81	*trans*-**2a**	67
2	CH_3O	3-furyl	allyl	*cis*-**1b**	68	*trans*-**2b**	44
3	CH_3O	3-furyl	benzyl	*cis*-**1c**	66	*trans*-**2c**	53
4	PhO	2-furyl	propargyl	*cis*-**1d**	78	*trans*-**2d**	48
5	PhO	2-furyl	3-butenyl	*cis*-**1e**	73	*trans*-**2e**	46
6	PhO	PMP[b]	benzyl	*cis*-**1f**	84	*trans*-**2f**	50
7	CH_3O	3-thienyl	allyl	*cis*-**1g**	98	*trans*-**2g**	50

[a] Yield of pure, isolated product with correct analytical and spectral data. [b] PMP = 4-$MeOC_6H_4$.

achieve *trans*-1,3,4-trisubstituted *β*-lactams in a convenient manner. As far as we know, these are the first examples of isomerization induced by heat in *β*-lactams.[17] This novel isomerization greatly extends the utility of the *cis*-stereoselective synthesis of 2-azetidinones via Staudinger reaction. We believed as well that our results may help to understand the studies on the origins of the stereodivergent outcome in the Staudinger reaction.

Starting substrates, racemic azetidinones **1a**−**g**, were obtained in good yields as single cis diastereoisomers by cyclization of alkoxyacetyl chlorides and imines in the presence of Et_3N. Our initial aim was to promote an intramolecular Diels−Alder reaction (IMDA) on substrate *cis*-**1e**, because we are currently involved in the synthesis of *β*-lactams related to trinems via IMDA of 2-azetidinone-tethered trienes.[14e,f] However, to our surprise, compound *trans*-**2e** was obtained instead of the expected cycloadduct. Toluene was chosen as the solvent because is the usual medium for our IMDA reactions since it is cheap and readily available. However, we carried out as well the reactions in other solvents such as chlorobenzene, mesitylene, and ethylbenzene. Chlorobenzene gave result similar to those of toluene, but slightly lower conversions were obtained using mesitylene and ethylbenzene. *cis*-2-Azetidinones **1a**−**g**, on heating in a sealed tube in toluene at 230 °C, were cleanly transformed into the isomeric *trans*-2-azetidinones **2a**−**g**.[18] The efforts made to follow the time course of the reaction showed that 16 h is a convenient endpoint, because extended reaction times did not improve the yield and after shorter reaction times large amount of unreacted starting material was recovered. Pure compounds were isolated in fair to good yields (46−67%) by flash chromatography (Table 1).[19] The assignment of the trans stereochemistry to *β*-lactams **2a**−**g** was based on the observed coupling constants of about 2.0 Hz for methine protons H3 and H4, whereas cis stereochemistry of the former cis stereoisomers **1a**−**g** was consistent with methine coupling constants of ca. 5.0 Hz in their ^1H NMR spectra.[20] This transformation tolerates different substituents at the 2-azetidinone ring. We believe that maybe an unprecedented thermally promoted C3−C4 bond cleavage occurs, followed by cyclization, being now the thermochemically more stable trans isomer preferentially formed. Our result can be tentatively interpreted as being involved a homolytic cleavage of the C3−C4 bond to afford an intermediate biradical **3**, that after bond rotation to give **4** and recombination would generate the *trans*-azetidinone. Taking into account the proposed reaction pathway, an aromatic substituent attached to the position 4 together with an alkoxy substituent attached to the position 3 of the four-membered ring that can stabilize the radical intermediates **3** and **4**, seems to be the driving force for isomerization (Scheme 1). Alternatively may be involved the open-chain zwitterionic intermediates **5** and **6**, leading to the corresponding *trans*-*β*-lactam through an electrocyclic conrotatory ring closure of the azadiene **6**. An aromatic substituent attached to the position 4 of the four-membered ring may be assumed to stabilize the positive charge in the zwitterionic intermediates **5** and **6** (Scheme 1). According to the accepted model for Staudinger reaction, (*E*)-imines lead preferentially to the more hindered *cis*-*β*-lactams.[21] It may be possible that

Scheme 1



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(18) When the experiments were performed at lower temperature unreactive *cis*-2-azetidinones were observed. Complex reaction mixtures were detected when the reactions were carried out at higher temperatures.

(19) The moderate yields obtained in some cases result from incomplete conversion of the starting material together with unidentified side reaction products.

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at high temperature the torquoelectronic effects inducing preferential or exclusive formation of the cis cycloadducts on the Staudinger reaction[22] are overwhelmed, as it appears that the stereochemistry of the process is now being governed by the thermodinamic stability of the formed products. This behavior may be explained, in an oversimplification, as a dominance of steric effects on electronic torquoselectivity.

In conclusion, we have developed an unprecedented thermally induced single-pot conversion method for switching the stereochemistry of the 4-aryl-β-lactam ring from cis to trans. This further expands the utility of the most important and direct route to 2-azetidinones, the usually *cis*-stereoselective Staudinger reaction. This new isomerization reaction complements others existing methods for the direct preparation of *trans*-β-lactams. Current work is directed toward the introduction of a chiral auxiliary, which will allow the asymmetric version of this novel isomerization reaction.

Experimental Section

General Methods. General experimental data and procedures have been previously reported.[14a] NMR spectra were recorded in $CDCl_3$ solutions, except as otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 77.0 ppm). All commercially available compounds were used without further purification. The *cis*-1-(benzyl)-4-(*p*-methoxyphenyl)-3-phenoxy-2-azetidinone **1f** was prepared according to our previously reported procedure.[14a]

Thermally Promoted Isomerization Reaction of *cis*-2-Azetidinones 1a−g. General Procedure for the Synthesis of *trans*-2-Azetidinones 2a−g. A solution of the corresponding *cis*-2-azetidinone **1** (0.40 mmol) in toluene (5 mL) was heated in a sealed tube at 230 °C for 16 h. The reaction mixture was allowed to cool to room temperature, the solvent was removed under reduced pressure, and after flash chromatography eluting with hexanes/ethyl acetate, the appropriate *trans*-2-azetidinone **2** was obtained. Spectroscopic and analytical data for some representative pure forms of **2** follow.[23]

***trans*-1-(3-Butenyl)-4-(3-furyl)-3-methoxy-2-azetidinone, 2a.** From 50 mg (0.18 mmol) of *cis*-2-azetidinone **1a** was obtained 34 mg (67%) of compound **2a** as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate 3/1). ^{1}H NMR: δ 2.91 (m, 2H), 2.85 and 3.47 (m, each 1H), 3.44 (s, 3H), 4.31 (d, 1H, J = 1.2 Hz), 4.42 (d, 1H, J = 1.2 Hz), 5.03 (m, 2H), 5.66 (m, 1H), 6.29 (d, 1H, J = 1.4 Hz), 7.41 (m, 2H). ^{13}C NMR: δ 166.5, 144.2, 140.5, 134.5, 121.4, 108.0, 89.8, 57.6, 54.6, 39.2, 29.5. IR ($CHCl_3$): ν 1750. MS (EI) *m*/*z*: 222 (M^+ + 1, 21), 221 (M^+, 100). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 5.02; N, 4.65. Found: C, 65.24; H, 5.11; N, 4.75'.

***trans*-3-Methoxy-1-(2-propenyl)-4-(3-thienyl)-2-azetidinone, 2g.** From 67 mg (0.30 mmol) of *cis*-2-azetidinone **1g** was obtained 35 mg (50%) of compound **2g** as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate 2/1). ^{1}H NMR: δ 3.38 (dd, 1H, J = 15.0, 6.8 Hz), 3.53 (s, 3H), 4.15 (dd, 1H, J = 15.0, 5.4 Hz), 4.41 (d, 1H, J = 1.5 Hz), 4.61 (d, 1H, J = 1.5 Hz), 5.14 (ddd, 2H, J = 16.6, 10.3, 1.4 Hz), 5.71 (m, 1H), 7.01 (d, 1H, J = 5.4 Hz), 7.24 (dd, 1H, J = 3.0, 1.0 Hz), 7.38 (d, 1H, J = 2.1 Hz). ^{13}C NMR: δ 166.5, 137.9, 131.0, 127.3, 125.3, 123.1, 119.7, 90.7, 77.4, 58.3, 42.8. IR ($CHCl_3$): ν 1747. MS (CI) *m*/*z*: 224 (M^+ + 1, 100), 223 (M^+, 30). Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.29; H, 5.95; N, 6.17; S, 14.24.

Acknowledgment. Support for this work by the DGES-MEC (Project PB96-0565) is gratefully acknowledged.

Supporting Information Available: Spectroscopic and analytical data for isomerically pure compounds **1a**−**g**, and **2b**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000229X

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(23) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.