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Stereoselective synthesis of new β-lactams by cyclocondensation of 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene with 4-formyl substituted azetidinones☆

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Abstract

The $BF_3 \cdot OEt_2$ or $LiClO_4$ catalyzed hetero Diels–Alder reaction of 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) with enantiomerically pure 4-formylazetidin-2-ones affords the corresponding cycloadducts in fair to good yields and in diastereoisomeric ratios of up to 98:2. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: β-Lactams; Hetero Diels–Alder cycloaddition; Stereoselectivity

1. Introduction

The well-recognized importance of β-lactams as therapeutic agents continuously stimulates the pharmaceutical industry to develop new derivatives of this class of compounds possessing broader spectra of activity and better properties with respect to biological resistance and chemical degradation [1]. As a consequence, there is a growing interest in synthetic methods that allow construction and modification of the 2-azetidinone ring in a mild and selective fashion.

In this context, 4-formyl substituted azetidin-2-ones recently emerged as versatile building blocks for the assembly of important bio-active β-lactams and of a variety of acyclic derivatives thereof [2]. We here describe a novel reaction of this class of compounds, namely their Lewis acid (LA) promoted cyclocondensation with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) [3] to stereoselectively afford previously unreported 4-[(2,3-dihydro-4-pyranon)-2-yl]-substituted β-lactams.

2. Results

Aldehydes (*R*)-**1**, (3*S*,4*R*)-**2**, and (3*R*,4*R*)-**3** were selected as representative starting materials because they feature different substitution patterns at C-3 and different relative configurations at C-3 and C-4 of the β-lactam ring. They were prepared in three steps by condensation of the titanium enolates of 2-pyridylthioesters with the (*S*)-*N*-benzylimine (**4**) derived from (*R*)-cyclohexylidene glyceraldehyde [4], followed by diol deprotection with trifluoroacetic acid (TFA) in water, and oxidative degradation ($NaIO_4$) [2,5].

The aldehydes were reacted with 4 mol. equiv. of Danishefsky's diene **5** in the presence of $BF_3 \cdot OEt_2$ (in CH_2Cl_2 at -78°C) or $LiClO_4$ (in CH_2Cl_2 [6] or Et_2O [7] at room temperature (r.t.)) to give, after acidic work up (TFA in CH_2Cl_2, 15 h, r.t.), cycloadducts **6a,b–8a,b** as mixtures of diastereoisomers (Scheme 1). Reaction conditions, yields, and diastereoisomeric ratios (d.r.) are reported in Table 1. The d.r. were determined by 300 MHz ^{1}H NMR analysis of the crude reaction mixtures, and were confirmed upon separation of the products by flash chromatography.

Aldehyde **1** reacted in a highly stereoselective fashion in the presence of $BF_3 \cdot OEt_2$ to give cycloadduct **6a** as a single isomer in moderate yield. The $LiClO_4$ promoted cyclocondensations of the same aldehyde carried out in different reaction conditions were both less

☆ Dedicated to Professor Antonio Maccioni, Universitá di Cagliari, on the occasion of his 75th birthday.

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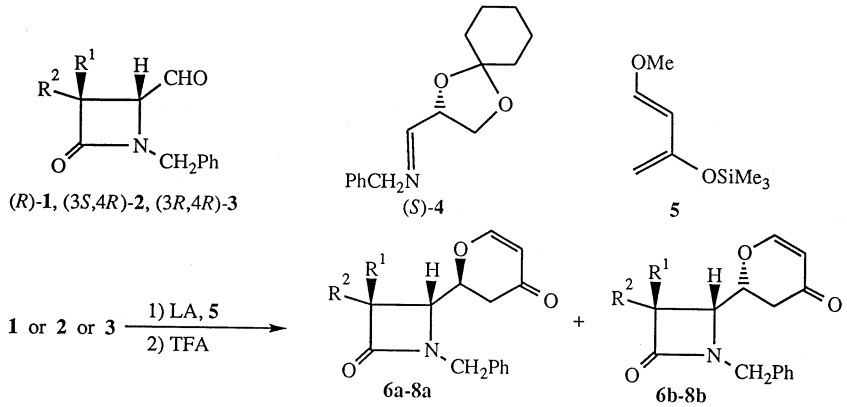


Scheme 1. Synthesis of cycloadducts **6–8** from aldehydes **1–3** and diene **5**.

Table 1
Stereoselective synthesis of cycloadducts **6–8** in different reaction conditions

Aldehyde[a]	LA (mol. equiv.)[b]	Solvent	Product	Yield (%)[c]	**a:b** ratio[d]
1	$BF_3 \cdot OEt_2$ (1.0)	CH_2Cl_2	**6a,b**	43	>98:2
1	$LiClO_4$ (0.1)	CH_2Cl_2	**6a,b**	39	75:25
1	$LiClO_4$ (1.0)	CH_2Cl_2	**6a,b**	41	75:25
1	$LiClO_4$ (2.0)	Et_2O	**6a,b**	35	70:30
2	$BF_3 \cdot OEt_2$ (1.0)	CH_2Cl_2	no reaction		
2	$LiClO_4$ (0.1)	CH_2Cl_2	**7a,b**	30	18:82
2	$LiClO_4$ (1.0)	CH_2Cl_2	**7a,b**	55	56:44
2	$LiClO_4$ (2.0)	Et_2O	**7a,b**	60	50:50
3	$BF_3 \cdot OEt_2$ (1.0)	CH_2Cl_2	**8a,b**	45	>98:2
3	$LiClO_4$ (0.1)	CH_2Cl_2	**8a,b**	29	65:35
3	$LiClO_4$ (1.0)	CH_2Cl_2	**8a,b**	74	12:88
3	$LiClO_4$ (2.0)	Et_2O	**8a,b**	67	56:44
3	$MgBr_2 \cdot OEt_2$ (0.1)	CH_2Cl_2	**8a,b**	53	60:40

[a] Aldehyde:diene ratio is 1:4.
[b] $BF_3 \cdot OEt_2$ reactions at −78°C; $LiClO_4$ reactions at r.t.
[c] Isolated yields.
[d] As determined by 300 MHz ^1H NMR spectroscopy on the crude products.

yielding and less stereoselective, and led to the preferential formation of the same diastereoisomer, namely **6a**.

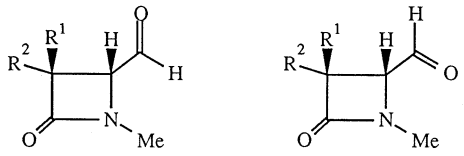
Only $LiClO_4$ was effective as LA in the reactions of aldehyde **2**, but in this case the stereochemical outcome was unpredictable. Indeed, adducts **7b** was obtained as the major isomer in the catalyzed (0.1 mol. equiv. of LA) reaction in CH_2Cl_2, while the promoted (1.0 mol. equiv. of LA) cyclocondensations either in CH_2Cl_2 or in Et_2O were virtually stereorandom.

The high diastereoselectivity observed in the $BF_3 \cdot OEt_2$ promoted reaction of aldehyde **1** was maintained also for aldehyde **3**, from which adduct **8a** was obtained as a single isomer. Also in this case the stereochemical outcome of the $LiClO_4$ promoted cycloadditions was unpredictable: opposite isomers of **8** were obtained as major products in CH_2Cl_2, while a less stereoselective reaction was observed in Et_2O.

The presence of a benzyloxy group in the *cis* configurated β-lactam **3** suggested the use of $MgBr_2 \cdot OEt_2$ as a chelating catalyst [8]. However, this reaction showed poor stereoselectivity (d.r. = 60:40) in favor of isomer **8a**, the same obtained employing non chelating $BF_3 \cdot OEt_2$.

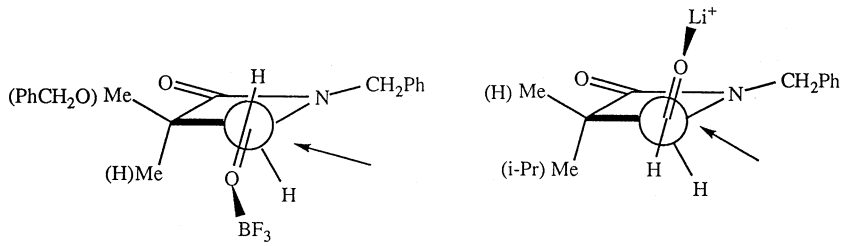
In summarizing the experimental results, one can say that

1. when effective, $BF_3 \cdot OEt_2$ is the LA of choice for these reactions, at least in terms of stereoselectivity,
2. $LiClO_4$ is a more general promoter, but its use leads to lower and unpredictable stereocontrol, and
3. the use of $LiClO_4$ in Et_2O is detrimental for the stereoselection of the cyclocondensation reaction.

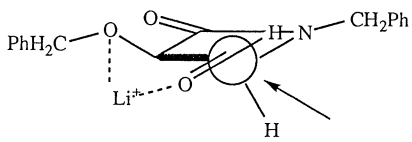


s-trans **9-11** *s-cis* **9-11**

9: $R^1=R^2=H$; **10:** $R^1=R^2=Me$; **11:** $R^1=H$, $R^2=MeO$



Model **A** Model **B**



Model **C**

Scheme 2. Structure of model compounds **9–11**, and model of stereoselection **A–C**.

3. Discussion

Any attempt of rationalization of these results necessarily requires a secure assignment of the absolute stereochemistry to **6a,b–8a,b**. However, this could not be achieved unambiguously either by chemical correlation or by spectroscopic means. For instance, the HC-4/HC-4′ coupling constants and the chemical shift trends of these protons were not trusted to be diagnostic of the relative configuration at these stereocenters. A tentative attribution based on mechanistic considerations and comparison with the steric course of related reactions is therefore proposed.

Experimental results reported in the literature show that (i) 4-formyl substituted β-lactams as **1–3** undergo nucleophilic attack by a Grignard reagent on the aldehyde *Si* face from the side of the hydrogen at C-4 to give the C-4/C-4′ *anti* product in a higly stereoselective fashion [2]; and (ii) the benzyl- and electron withdrawing group-substituted nitrogen atom in **1–3** cannot restrain the conformational mobility around the C-4/CHO bond by giving rise to a chelated complex involving the LA [3,9]. Therefore, the sense of stereoselectivity of the cyclocondensation is likely to be a direct consequence of the conformational preference around the C-4/CHO bond in the LA complexed aldehydes. This preference was determined by computational methods (see Section 5) studying aldehydes **9–11** and their BF_3 and Li^+ complexes as simplified models of **1–3** (Scheme 2).

The *s-trans* conformation of the uncomplexed aldehydes was found to be more stable than the *s-cis* one by 0.6, 0.5 and 0.7 kcal/mol for **9**, **10** and **11**, respectively. Upon complexation with BF_3 the energy gap between the *s-trans* and the *s-cis* conformers widened to become 1.1, 1.0 and 1.3 kcal/mol for $\mathbf{9}\cdot BF_3$, $\mathbf{10}\cdot BF_3$ and $\mathbf{11}\cdot BF_3$, respectively.

Thus, it seems reasonable that in the presence of $BF_3\cdot OEt_2$ the aldehydes **1** and **3** undergo attack from the side of the hydrogen at C-4 on the carbonyl *Si* face in their *s-trans* conformations to preferentially afford C-4/C-4′ *anti* products **6a** and **8a**, respectively. The formation of the *anti* isomers is also in agreement with the steric course of the cyclocondensation of diene **5** with chiral α-aminoaldehydes bearing a benzyl and an electron withdrawing group as nitrogen substituents as in **1–3** [3,9].

Model **A** (Scheme 2) could be used as a working hypothesis to tentatively account for the observed sense of stereoselectivity. This rationale, however, does not explain why aldehyde **2** does not react with diene **5** in the presence of $BF_3\cdot OEt_2$.

The computational analysis of the $\mathbf{9–11}/Li^+$ complexes was less conclusive. Firstly, it must be mentioned that a very stable *s-cis* conformation in which the aldehyde oxygen and the β-lactam nitrogen are chelated by Li^+ was found on the potential energy surface. However, the calculations are run in vacuum and thus the electrostatic interactions between the azetidi-

none nitrogen and the lithium cation are likely to be artificially maximized. This conformation, that has little chemical significance because the nitrogen atom is not coordinating [3,9], was therefore disregarded.

For the **9**/Li^+ and the **10**/Li^+ complexes, the more plausible, non-chelated *s-cis* conformations were found to be only slightly more stable (0.5 kcal/mol) than the *s-trans* ones. This reduced energy difference indicates a limited conformational preference around the C-4/CHO bond, and can well account for the poorer stereocontrol of the $LiClO_4$ promoted reactions of **1** and **2**. Attack of diene **5** from the side of the hydrogen at C-4 on the *Re* face of the Li^+-complexed aldehydes **1** and **2** in their *s-cis* conformation, as depicted in model **B**, can explain the formation of the *syn* isomers **6b** and **7b**. The different stereochemical outcome observed when the cycloadditions were run with different amounts of LA and in solvents of different coordinating ability (such as CH_2Cl_2 and Et_2O) are beyond our rationalization efforts.

For the aldehyde-**11**/Li^+ complex (and, possibly, for the aldehyde-**3**/Li^+ complex as well) the existence of an *s-trans* conformation in which the oxygen atoms of the aldehyde and of the C-3 alkoxy group are locked by Li^+ to form a six-membered chelate is chemically plausible and was clearly shown by the calculations. This conformation was calculated to be more stable than the *s-cis* one by as much as 3.5 kcal/mol (an energy difference that can well be overestimated, see above) and is reported in model **C**.

The formation of the *anti* isomer **8a** can be explained by attack from the less hindered side on the aldehyde *Si* face. The formation of the *syn* product **8b** can arise either from an unlikely attack on the aldehyde *Re* face in the same conformation, or, better, by attack from the side of the hydrogen at C-4 on an *s-cis* conformation similar to **B**, that however should be considerably more populated than it is predicted by the calculations.

4. Conclusions

In conclusion, the synthesis of some novel β-lactams by the hetero Diels–Alder cyclocondensation of enantiomerically pure 4-formyl substituted azetidin-2-ones with Danishefsky's diene has been accomplished. In some cases high levels of stereoselectivity were obtained (d.r. of up to 98:2). The steric course of the reaction has been discussed and the configurations of the products tentatively assigned on the basis of mechanistic considerations and semi-empirical MO calculations.

5. Experimental

5.1. Synthesis of aldehydes *1–3*

Aldehydes **1–3** were obtained following a previously described procedure [2]. Compound **3** has already been reported [2].

5.1.1. (4R)-1-Phenylmethyl-3,3-dimethyl-4-formyl-azetidin-2-one (*1*)

Compound **1** (68% yield) was an oil: $[\alpha]_D^{23}$ −27.5° (*c* 1, $CHCl_3$). IR: *v* 1755, 1735 cm^{-1}. ^1H NMR: δ 9.50 (1H, d, *J* 2.9 Hz); 7.15–7.40 (5H, m); 4.71 (1H, d, *J* 14.5 Hz); 4.32 (1H, d, *J* 14.5 Hz); 3.60 (1H, d, *J* 2.9 Hz); 1.40 (3H, s); 1.12 (3H, s). *Anal.* Calc. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.59; H, 7.07; N, 6.57%.

5.1.2. (3S, 4R)-1-Phenylmethyl-3-(1-methylethyl)-4-formylazetidin-2-one (*2*)

Compound **2** (66% yield) was an oil: $[\alpha]_D^{23}$ −24.7° (*c* 1, $CHCl_3$). IR: *v* 1755, 1735 cm^{-1}. ^1H NMR: δ 9.40 (1H, d, *J* 2.9 Hz); 7.15–7.40 (5H, m); 4.65 (1H, d, *J* 16.9 Hz); 4.25 (1H, d, *J* 16.9 Hz); 3.55 (1H, dd, *J* 2.9, 2.5 Hz); 2.98 (1H, dd, *J* 7.0, 2.5 Hz); 0.80–1.30 (7H, m). *Anal.* Calc. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.57; H, 7.27; N, 5.99%.

5.2. Cyclocondensation reaction: general procedure

To a stirred 0.1 M solution of aldehyde (0.5 mmol) in dry solvent (5 ml) kept under nitrogen at the indicated temperature, commercially available diene **5** (2 mmol, 0.2 ml) dissolved in 2 ml of solvent was added in one portion. The LA was then added and the mixture stirred for 4 h. Another portion of diene was then added as before, and the mixture stirred overnight. The reaction was quenched by addition of 10 ml of a saturated aqueous solution of $NaHCO_3$, and the aqueous phase was extracted twice with 20 ml portions of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuum. The crude residue was taken up in 10 ml of CH_2Cl_2 and treated with TFA (0.5 mmol, 0.038 ml) for 15 h at r.t. A total of 10 ml of a saturated aqueous solution of $NaHCO_3$ were then added, and the aqueous phase was extracted twice with 20 ml portions of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuum. The crude residue was analyzed by 300 MHz ^1H NMR spectroscopy to assess the d.r., and then was purified by flash chromatography over silica gel with Et_2O as eluant to give the products as differently enriched mixtures of diastereoisomers in the yields and d.r. reported in Table 1. They were thick oils that solidified when stored at −20°C.

*5.2.1. 1-Phenylmethyl-3,3-dimethyl-4-[(2,3-dihydropyran-4-on)-2-yl]-azetidin-2-one (**6a,b**)*

IR: ν 1755, 1680, 1600 cm^{-1}. *Anal.* Calc. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.27; H, 6.54; N, 5.06%. Selected ^1H NMR of **6a**: δ 7.28 (1H, d, *J* 6.0 Hz, OCH=); 5.41 (1H, d, *J* 6.0 Hz, HC=CO); 4.52 (1H, m, HC–O); 3.31 (1H, d, *J* 6.0 Hz, H-C4); 2.47 (2H, AB system, CH_2C=O); 1.40 (3H, s, Me); 1.11 (3H, s, Me). Selected ^1H NMR of **6b**: δ 7.28 (1H, d, *J* 6.0 Hz, OCH=); 5.41 (1H, d, *J* 6.0 Hz, HC=CO); 4.52 (1H, m, HC–O); 3.25 (1H, d, *J* 7.0 Hz, H-C4); 2.47 (2H, AB system, CH_2C=O); 1.40 (3H, s, Me); 1.11 (3H, s, Me).

*5.2.2. 1-Phenylmethyl-3-(1-methylethyl)-4-[(2,3-dihydropyran-4-on)-2-yl]-azetidin-2-one (**7a,b**)*

IR: ν 1755, 1680, 1600 cm^{-1}. *Anal.* Calc. for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.55; H, 6.96; N, 4.60%. Selected ^1H NMR of **7a**: δ 7.27 (1H, d, *J* 6.0 Hz, OCH=); 5.40 (1H, d, *J* 6.0 Hz, HC=CO); 4.44 (1H, m, HC–O); 3.44 (1H, dd, *J* 6.0, 2.5 Hz, H-C4); 2.67 (1H, dd, *J* 7.0, 2.5 Hz, H-C3). Selected ^1H NMR of **7b**: δ 7.27 (1H, d, *J* 6.0 Hz, OCH=); 5.41 (1H, d, *J* 6.0 Hz, HC=CO); 4.45 (1H, m, HC–O); 3.43 (1H, dd, *J* 6.0, 2.5 Hz, H-C4); 2.93 (1H, dd, *J* 7.0, 2.5 Hz, H-C3).

*5.2.3. 1-Phenylmethyl-3-phenylmethoxy-4-[(2,3-dihydropyran-4-on)-2-yl]-azetidin-2-one (**8a,b**)*

IR: ν 1750, 1685, 1600 cm^{-1}. *Anal.* Calc. for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.49; H, 5.83; N, 3.74%. Selected ^1H NMR of **8a**: δ 7.27 (1H, d, *J* 6.2 Hz, OCH=); 5.40 (1H, d, *J* 6.2 Hz, HC=CO); 4.75 (1H, m, HC–O); 4.65 (1H, d, *J* 5.2 Hz, H-C3); 3.75 (1H, d, *J* 6.0, 5.2 Hz, H-C4); 2.67 (2H, AB system, CH_2C=O). Selected ^1H NMR of **8b**: δ 7.27 (1H, d, *J* 6.2 Hz, OCH=); 5.47 (1H, d, *J* 6.2 Hz, HC=CO); 4.73 (1H, d, *J* 5.0 Hz, H-C3); 4.47 (1H, m, HC–O); 3.92 (1H, d, *J* 6.0, 5.2 Hz, H-C4); 2.67 (2H, AB system, CH_2C=O).

5.3. Calculations

All calculations were performed at semiempirical level using the MNDO hamiltonian as implemented in MOPAC 6.0 (J.J.P. Stewart, QCPE Program No. 455). All stationary points located on the potential energy surfaces were characterized as true minima by performing a complete vibrational analysis. The calculations were performed by using a Vax Station 3100 and a Microvax 3100 (Digital).

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