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Highly Diastereoselective Allylic Azide Formation and Isomerization. Synthesis of 3(2′-Amino)-β-lactams

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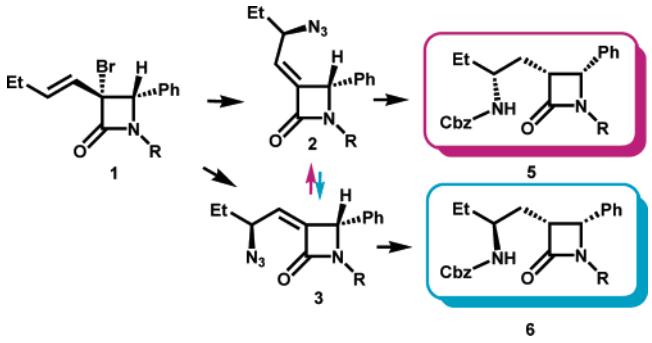
ABSTRACT



The stereoselective anti S_N2' attack of NaN_3 to 3-alkenyl-3-bromo-azetidin-2-ones gave a mixture of diastereomeric azides in fast equilibrium. The [3,3]-sigmatropic rearrangement of allylic azides occurred with complete stereocontrol, allowing the equilibrium to be directed preferentially toward the (*E*)- or (*Z*)-isomer, useful precursors of 3(2′-amino)-β-lactams.

One of the most useful reactions in organic chemistry is the nucleophilic substitution of allylic halides. Many important aspects of their behavior such as the stereo- and regiochemistry of the substitutions, have received considerable attention.[1]

The reaction of a nucleophile upon an allylic halide can occur via an S_N2 process with attack at Cα or through an S_N2' process with attack of the nucleophile at Cγ and departure of the leaving group. While the stereochemistry of the S_N2 is defined, the S_N2' attack can occur syn or anti with respect to the leaving group, depending on the nature of the nucleophile.[1a−c] The theory[2] suggests that a syn process is to be predicted for neutral nucleophiles, while anionic nucleophiles approach from the anti direction; however, the experimental evidence "is often contradictory".[1a] This paper concerns the nucleophilic attack of NaN_3 to a particular allylic moiety, the 3-alkenyl-3-bromo-azetidin-2-ones **1**.[3]

This reaction shows interesting mechanistic aspects[4] and offers the opportunity to introduce in few steps and under high regio- and stereocontrol the amino function in the side

(1) For a review, see: (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901−1930. (b) Toromanoff, E. *Tetrahedron* **1980**, *36*, 2809−2931. (c) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383−7423. For recent reviews on metal-catalyzed allylic substitution reactions, see: (d) Pfaltz, A.; Lautens, M., In *Comprehensive Asymmetric Catalysis II;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag Telos: Berlin Heidelberg, 1999; Chapter 24, pp 833−884. (e) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943.

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chain of the β-lactam[5] (Figure 1). The propensity of allylic azides to undergo [3,3]-sigmatropic rearrangement,[6] thus

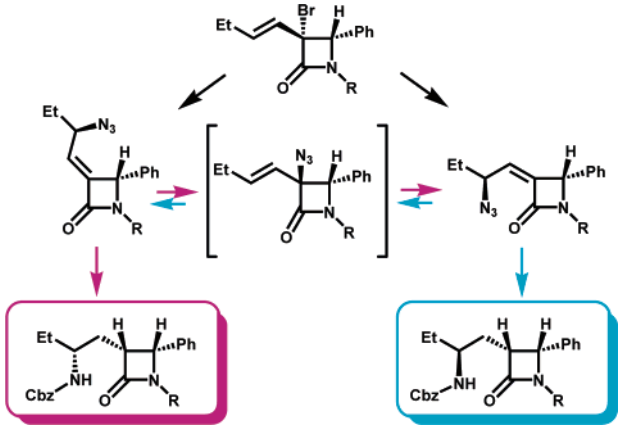


Figure 1. Synthetic pathway to 3(2′-amino)-β-lactams.

giving a mixture of isomers, is overcome in our case by the complete stereocontrol at the equilibrium, which makes the reaction of synthetic interest.[7]

In 1971, Bose and Manhas[8] described the direct synthesis of α-vinyl-β-lactams by the reaction of crotonyl chloride and TEA with a Schiff base. We have applied the same reaction conditions for the preparation of 3-alkenyl-3-bromo-azetidin-2-ones,[3] starting from α-bromo-β,γ-unsaturated ketenes[9] and a variety of Schiff bases. The reaction occurs smoothly in moderate to good yields (50−60%), affording preferentially the cis diastereomers, which were purified by flash chromatography or preparative HPLC and utilized as starting materials for further transformations. The prospects of the employment of α-alkenyl-α-bromo-azetidin-2-ones **1** as precursors of new molecules, prompted us to verify the feasibility of the substitution reaction. The presence of the allylic bromide permitted easy S_N2' reaction. In fact, the treatment of *cis*-(±)-**1a**−**c** and (1′*S*,3*R*,4*S*)-**1d** with NaN_3 in DMF at 70 °C afforded 1:1 mixtures of (*E*)-**2** and (*Z*)-**3** azido derivatives in good yield[10] (Table 1) and 10−15% yield of

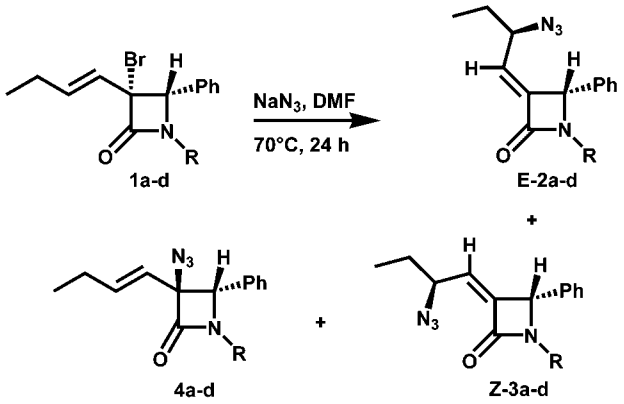
Table 1. Nucleophilic Attack of NaN_3 to 3-Bromo-3-alkenyl-azetidin-2-ones (±)-**1a**−**d** in DMF at 70 °C

1	R	yield[a] of (*E*)-**2** + (*Z*)-**3** (%)	dr of **E**[b] (%)	dr of **Z**[b] (%)
1a	CH_2Ph	69	92:8	85:15
1b	$C_2H_4CO_2Et$	78	>95:5	>95:5
1c	$CH_2CH{=}CH_2$	70	85:15	88:12
1d	(*S*)-phenylethyl-	68	90:10	90:10

[a] After purification by flash chromatography over silica gel. [b] Product distribution was determined by ^{1}H NMR integration at 300 MHz on the crude mixture and confirmed by isolation of pure compounds.

azide **4**[11] (Scheme 1). All the products were isolated by flash chromatography on silica gel. The *Z* and *E* configuration of

Scheme 1. Nucleophilic Attack of NaN_3 to 3-Bromo-3-alkenyl-azetidin-2-ones (±)-**1a**−**d**



the double bond was attributed by comparison of the chemical shift of vinyl proton H_1. In accordance with literature data,[12] the vinyl proton resonating at 5.25 ppm was attributed to the (*Z*)-**3** isomer, while the one at 6.0 ppm was attributed to the isomer (*E*)-**2**. Compounds **2** and **3** were obtained, as oils, in high diastereomeric ratio, each (*E*)-**2** or (*Z*)-**3** being accompanied by small amounts of the diastereoisomer with the C−N_3 stereocenter in the opposite configuration (Table 1, columns 4 and 5). In accordance with the theory on the S_N2' process for anionic nucleophiles, we suggest for optically active (*E*)-**2d** major isomer the (2′*R*) configuration and for the (*Z*)-**3d** major isomer the (2′*S*) configuration. To confirm the correct attribution of the stereochemistry, compound (±)-**1e** was prepared starting from benzyl-(4-nitro-benzylidene)-amine and α-bromo-hexenoyl chloride and obtained in 93% yield (Scheme 2). The

(5) For an example of azetidinone substituted at the side chain with an amino group such as tabtoxin and its analogues, see: (a) Lee, D. L.; Rapoport, H. *J. Org. Chem.* **1975**, *40*, 3491−3496. (b) Baldwin, J. E.; Otsuka, M.; Wallace, P. M. *Tetrahedron* **1986**, *42*, 3097−3110. (c) Greenlee, W. J.; Springer, J. P.; Patchett, A. A. *J. Med. Chem.* **1989**, *32*, 165−170.

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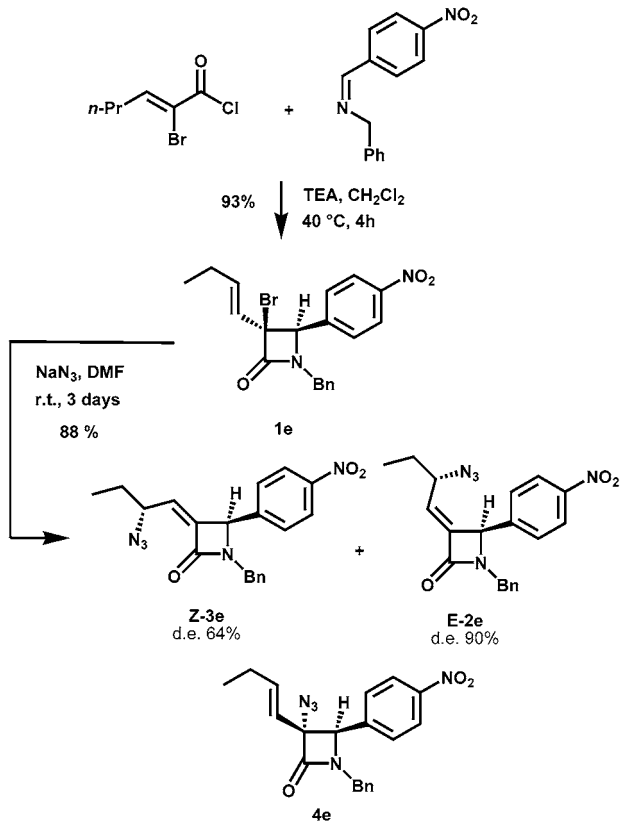
(10) Reaction of **1a** carried out at rt afforded, in about 70 h, (*E*)-**2a** as the major isomer (56%), (*Z*)-**3a** (29%), and **4a** (15%).

(11) Trans configuration of compound **4** was determined on the basis of the ^{1}H NMR signal of H1′ resonating at 5.0 ppm; see Supporting Information.

(12) (a) Anklam, S.; Liebscher, J. *Tetrahedron* **1998**, *54*, 6369−6384. (b) Otto, H. H.; Bergmann, H. J.; Mayrhofer, R. *Arch. Pharm. (Weinheim, Ger.)* **1986**, *319*, 203−216.

Scheme 2. Synthesis of 3-Bromo-3-alkenyl-azetidin-2-ones **1e** and Nucleophilic Attack of NaN_3



presence of the nitro group on the aromatic ring generally favors the crystallization of products. The S_N2' reaction, performed on azetidin-2-one (±)-**1e**, gave the products **2e**/**3e**/**4e** in 52/33/15 ratio and 88% total yield. The (*Z*)-isomer was obtained as an 82:18 mixture of diastereoisomers with opposite configuration at the C2′ stereocenter. Only the minor (*Z*)-isomer could be crystallized from methanol/water solution, and the X-ray analysis[13] showed the (2′*S**-*Z*,4*R**) relative configuration (Figure 2), thus allowing the (2′*R**-*Z*,4*R**) relative configuration to be attributed to the major isomer (*Z*)-**3e**. On the basis of these results, the anti direction of the nucleophile with respect to the bromide leaving group was confirmed.[2]

Comparison of the ^{1}H NMR chemical shift for (*E*)-**2a**−**e** and (*Z*)-**3a**−**e** series revealed a complete regularity and allowed us to determine the relative configuration. Furthermore, since compounds **2** and **3** are in equilibrium, we could establish, on the basis of the ^{1}H NMR analysis in $CDCl_3$, that this equilibrium involves the azide **4**. The slow equilibration between the three isomers was observed even at low temperature, changing the solvent (EtOAc) or in solvent-free conditions.

In fact, a mixture of **4e** (90%) and (*Z*)-**3e** (10%) was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR spectroscopy

(13) Crystal data for the minor (*Z*)-isomer: $C_{20}H_{19}N_5O_3$ MW = 377.40, monoclinic, $P2_1/n$, a = 15.8947(12) Å, b = 7.1605(6) Å, c = 17.1209(13) Å, β = 100.848(2)°, V = 1913.8(3) Å^3, Z = 4, D_{calcd} = 1.310 Mg/m^3, R_1 = 0.0676, wR_2 = 0.1297 (all data), GOF on F^2 = 1.037.

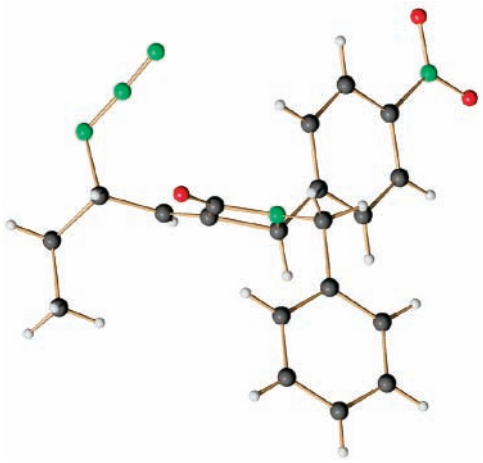


Figure 2. X-ray-determined structure for the minor (2′*S**-*Z*,4*R**)-**3e** diastereoisomer.

(Figure 3). The comparison of the spectra recorded at the initial time and after 24 h showed that the ratio between the products changed considerably, the amount of azide **4e** (33%) being decreased in favor of isomer (*Z*)-**3e** (63%) and (*E*)-**2e** (4%). In a similar way, pure (*E*)-**2e** in $CDCl_3$ converted in 72 h into a mixture of azide **4e** (15%), (*Z*)-**3e** (30%), and *E*-**2e** (55%).

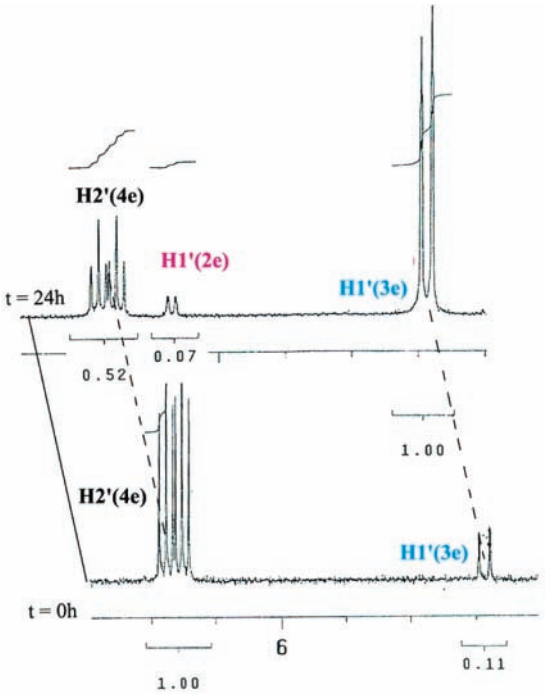
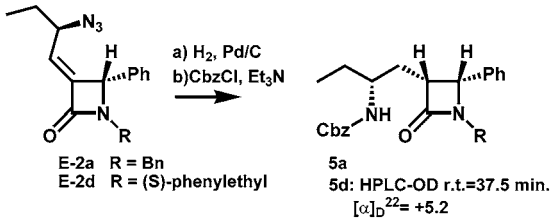


Figure 3. Comparison of ^{1}H NMR spectra of a mixture of **4e** and (*Z*)-**3e** at different times.

The complete selectivity of the rearrangement was confirmed by a sequence of reactions carried out both on racemic **2a** and on optically pure **2d**. To this aim, pure (*E*)-**2a** was

hydrogenated with Pd/C to the corresponding amino derivative, which was converted into the Cbz-derivative **5a** (overall yield = 68%) (Scheme 3). The 3,4-cis stereochemistry of

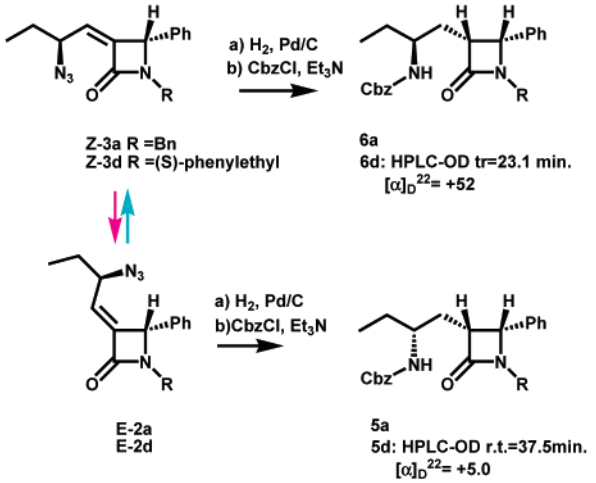
Scheme 3. Conversion of (*E*)-**2** into CBz-Derivative **5**



5a was assigned on the basis of the coupling constants H_3-H_4 (J = 5.3 Hz). In a similar way, the hydrogenation and protection of pure (2′*R*-*E*)-**2d** afforded **5d** ($[\alpha]_D^{22} = +5.2$, Chiralcel OD:[14] rt, 37.5 min) in 50% overall yield. On the other hand, a solution of pure (*Z*)-**3a** in $CHCl_3$ reached the 2:1 (*Z*)-**3a**/(*E*)-**2a** ratio after 24 h.

From this mixture (*E*)-**2a** was separated by flash chromatography and reduced under the above-reported conditions. The hydrogenation and the conversion to Cbz-derivative afforded **5a** as a single diastereoisomer, as confirmed by ^{1}H NMR and ^{13}C NMR spectra (Scheme 4).

Scheme 4. Conversion of (*Z*)-**3** into Cbz-Derivative **6**, Equilibration to (*E*)-**2**, and Conversion to Cbz-Derivative **5**



Moreover, the hydrogenation of the pure (*Z*)-**3a**, followed by protection with Cbz, afforded exclusively **6a** (overall yield 50%), thus showing that the configuration of the newly stereogenic center is opposite in **2a** and **3a**. The same reaction sequence, performed on the optically active azides (2′*S*-*Z*)-**3d** afforded exclusively (2′*S*)-**6d** (yield 50%, $[\alpha]_D^{22} = +52$, Chiralcel OD:[12] rt, 23.1 min). In a similar way, compound (2′*R*-*E*)-**2d**, obtained from equilibration of the (2′*S*-*Z*)-**3d** isomer and separation by flash chromatography, was converted exclusively into (2′*R*)-**5d** (yield 50%, $[\alpha]_D^{22} = +5.0$, Chiralcel OD:[12] rt, 37.5 min), thus confirming the stereochemical outcome of the equilibration.

The complete selectivity of the rearrangement was rationalized by the mechanism proposed in Figure 4, where a

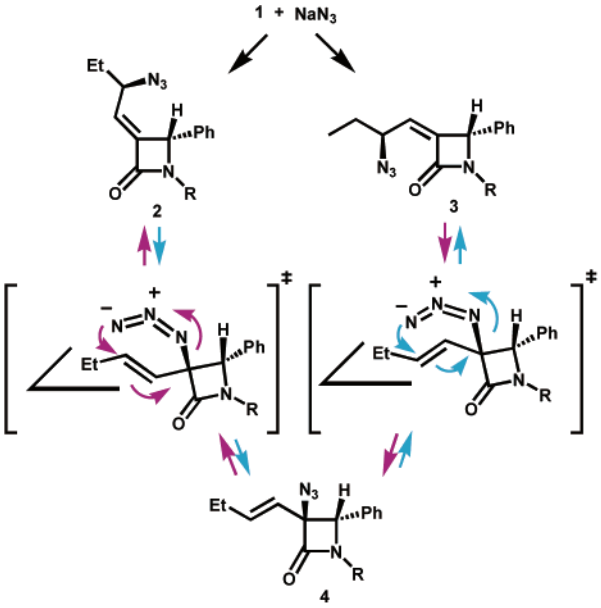


Figure 4. Mechanism proposed for the [3,3]-sigmatropic rearrangement.

concerted [3,3]-sigmatropic rearrangement occurs via a cyclic transition state with complete stereocontrol, in accordance with the mechanisms suggested for the interconversion of allylic azides.[4]

The (2′*R*-*E*)-**2**, generated by S_N2' attack on the *re* face of the double bond in **1**, is in equilibrium with *trans*-azide **4**, which converts to (2′*S*-*Z*)-**3** via [3,3]-sigmatropic shift on the *si* face of the double bond, with complete inversion of the C2′ configuration. In a similar way, the sodium azide S_N2' attack on the *si* face of the double bond in **1**, affords (2′*S*-*Z*)-**3**, which is in equilibrium with azide **4**.

In conclusion, we showed that the S_N2' azide attack occurs anti to the leaving bromide, in accordance with the theoretic suggestions. The equilibrium of the β-lactam double-bond occurs under complete stereocontrol via concerted [3,3]-sigmatropic rearrangement of the azide. Finally, the equilibrium (*E*)-**2**/(*Z*)-**3** or (*Z*)-**3**/(*E*)-**2** allows the use of this reaction for synthetic purposes, giving, after hydrogenation, stereodefined 3(2′-amino) derivatives.

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Supporting Information Available: Experimental procedures, full characterization of new compounds, and crystallographic data for the minor (*Z*)-isomer (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Optical rotation values in $CHCl_3$ (*c* 1.0); Chiralcel OD (Daicel column), cellulose tris(3,5-dimethyl-phenyl)carbamate phase coated on 10 μm silica gel, *n*-hexane/2-propanol 90:10 solvent mixture, flow 0.5 mL/min.