An Unprecedented Cleavage of the β-Lactam Ring: Stereoselective Synthesis of Chiral β-Amido Cyanides

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Summary: A new method has been developed for the synthesis of chiral β-amido cyanides by means of the regioselective cleavage of β-lactams in the presence of a TMSOTf catalyst and RCN.

The cleavage of the β-lactam ring has attracted much attention because suitably substituted β-lactams can be converted into compounds that are otherwise difficult to synthesize[1] and because many efficient, highly stereoselective syntheses of chiral β-lactam rings have been reported.[2] Recently, the use of β-lactams for generating valuable synthons via ring cleavage or ring expansion has been reviewed by Hesse[1b] and Manhas.[1c] Although most β-lactams undergo cleavage under mild conditions because of their strained structures, the main difficulty in the cleavage is control of the regioselectivity. The cleavage usually takes place at the 1,2- or 1,4-bond to give a COCCN or CCCON unit;[1] cleavages of the 2,3-[3] and 3,4-bonds[4] are not well-known processes.

As part of our research program directed toward the efficient substitution of 4-sulfinylazetidin-2-ones with silylated nucleophiles,[5,6] we recently reported a novel alkoxylation of 4-sulfinylazetidin-2-ones with tributyltin alkoxides.[7] Now, we report the novel formal cleavage of the 2,3-bond of 4-sulfinyl- and 4-alkoxyazetidin-2-ones 1 and 2 (Scheme 1).

The reactions of 4-sulfinylazetidin-2-one 1 (1 mmol) with trimethylsilyl alkoxides (Me_3SiOR^1, 3–5 mmol) in the presence of a catalytic amount of TMSOTf in acetonitrile

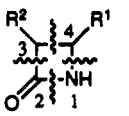


Figure 1.

Scheme 1

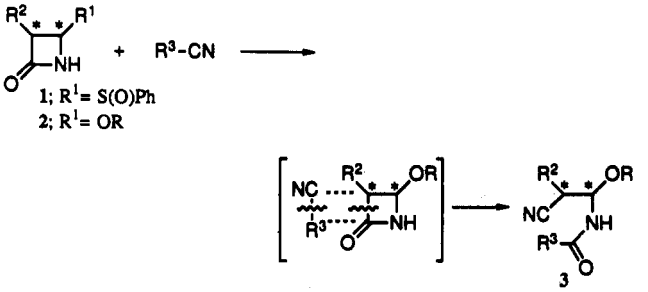
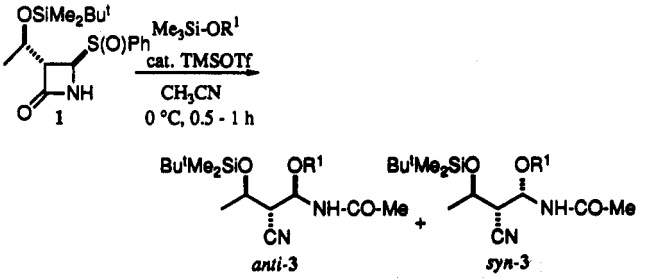


Table 1. β-Lactam Fragmentation of 4-Sulfinylazetidin-2-one 1



run	R^1	product 3	yield[a] (%)	ratio of *anti*:*syn*[b]
1	Me	**3a**	62	1.4:1[c]
2	Bn	**3b**	82	7:1
3	Pr	**3c**	52	2.2:1
4	cyclohexyl	**3d**	58	13:1

[a] After silica gel column chromatography. [b] Determined from ^{1}H-NMR data. [c] The low selectivity observed in run 1 was due to over reaction of 3 with excess Me_3SiOR^1.

(MeCN) at 0 °C for 0.5–1 h gave not expected 4-alkoxyazetidin-2-ones 2 but instead novel compounds 3 in good yields by means of alkoxylation at the 4-position, formal cleavage of the 2,3-bond, and recombination with the Me and CN units of acetonitrile (Table 1).

This unexpected and unprecedented reaction proceeded equally well with 4-alkoxyazetidin-2-ones **2a–e** and a catalytic amount of TMSOTf in acetonitrile. Furthermore, the reaction can be carried out not only in acetonitrile but also in other solvents containing a cyano group, such as propionitrile, butyronitrile, and benzonitrile (Table 2).[8] All reactions proceeded smoothly and stereoselectively.

Chiral β-amido cyanides 3 are quite useful compounds, since the *O*-methyl *N*,*O*-acetal unit of 3 can be used for C–C bond formation[9] and *O*-allylic compound **3h** can be used for the diastereoselective synthesis of β-(*N*-acylamino)aldehydes.[10]

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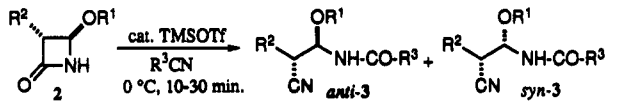
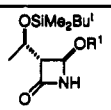
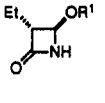
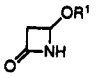
Table 2. β-Lactam Fragmentation of 4-Alkoxyazetidin-2-ones 2a–e



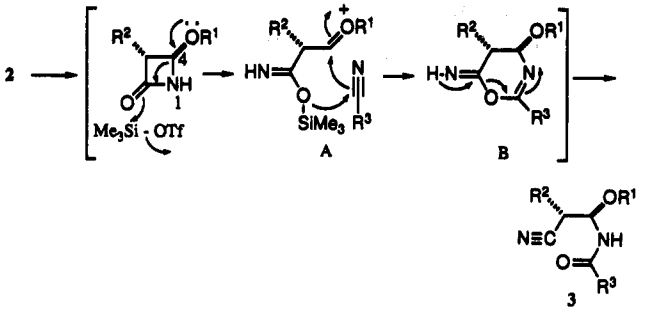
run		β-lactam 2	R1	R3	product 3	yield[a] (%)	ratio of anti:syn[b]
1	2a		Me	Me	3a	71	13:1
2	2a		Me	Et	3e	70	8:1
3	2a		Me	Pr	3f	90	5.7:1
4	2a		Me	Ph	3g	81	15:1
5	2b		allyl	Me	3h	81	4.6:1
6	2b		allyl	Pr	3i	66	14:1
7	2c		Me	Me	3j	82	1.2:1 (or 1:1.2)
8	2c		Me	Pr	3k	71	1.3:1 (or 1:1.3)
9	2c		Me	Ph	3l	61	1.2:1 (or 1:1.2)
10	2d		allyl	Me	3m	61	1.3:1 (or 1:1.3)
11	2e[c]		Me	Me	3n	69	

[a] After silica gel column chromatography. [b] Determined from ^{1}H-NMR data. [c] Racemic 2e was used.

The structure of 3 was determined from ^{1}H-NMR, ^{13}C-NMR, and IR data. An X-ray crystallographic structure of 3a shows that the major isomer is *anti* configured.[13]

The reaction presumably proceeds with the initial formation of oxonium ion A via 1,4-bond cleavage[11] and subsequent reaction with solvent (R^3CN) to give cyanide 3 via cyclic intermediate B (Scheme 2).

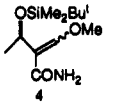
Scheme 2



Although several examples of the synthesis of cyanides via β-lactam cleavage have appeared in the literature,[12] most of the methods could not be applied to the synthesis of α-chiral cyanides because they would give α,β-unsaturated compounds. Our stereoselective fragmentation selectively gives α-chiral cyanides under mild conditions in good yields. Application of this methodology to various types of β-lactams is now under investigation.

Supplementary Material Available: Experimental procedures (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) When 2a was treated with a catalytic amount of TMSOTf in methylene chloride, olefin 4 was obtained via 1,4-bond cleavage.



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(13) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.