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Selective C-S Bond Cleavage of 3-Aryl-ß-sultams with $EtAlCl_2$

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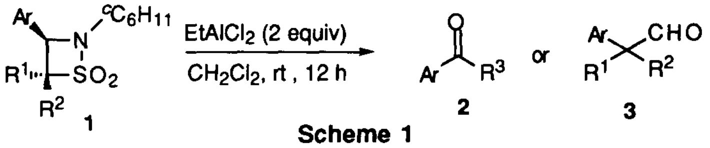
Abstract: Selective C-S bond cleavage of a ß-sultam ring was achieved by the reactions of 3-aryl-ß-sultams **1** with $EtAlCl_2$. Aryl ketones **2** or aldehyde **3** were provided *via* processes of the C-S bond cleavage, 1,2-aryl shift and imine formation. These reactions were influenced by the cation stabilizing capability of C-4 substituents and by the configuration of the substituents at C-3 and C-4.

1,2-Thiazetidine 1,1-dioxides (ß-sultams), sulfonyl analogues of ß-lactams, have a fixed and highly strained four membered ring with three different kinds of hetero single bonds, namely, C-N, C-S and N-S bonds. There have been reported several papers directed toward synthesis of potent drugs[1] and many papers on syntheses and reactions of ß-sultams with or without destruction of ß-sultam rings.[2] However, the reaction with the C-S bond cleavage has not been known. Recently we found that reactions of 3-aryl-ß-sultams with $EtAlCl_2$ caused regioselective C-S bond cleavage followed by 1,2-aryl shift to give aryl ketones or aldehyde. This paper describes the unprecedented transformation of 3-aryl-ß-sultams to aryl ketones or hindered aldehydes.

To optimize reaction conditions, we examined reactions of *cis*-2-cyclohexyl-3,4-diphenyl-ß-sultam (**1a**)[3] with some Lewis acids such as $EtAlCl_2$, $BF_3{\cdot}Et_2O$, $TiCl_4$, $Ti(O^iPr)_4$, $ZnCl_2$, ZnI_2 and $ZnEt_2$ and found that $EtAlCl_2$ is the mildest and most efficient reagent for the C-S bond cleavage. Reaction of **1a** with 1.1 equiv of $EtAlCl_2$ was carried out in CH_2Cl_2 under nitrogen at room temperature for 12 hours to give benzophenone (**2a**) in 56 % yield with 12 % of **1a** (Table 1, entry 1). Yield of **2a** increased to 81 % by use of 2 equiv of $EtAlCl_2$ (entry 2). A general procedure is as follows: To a stirred solution of a ß-sultam **1** (1 mmol) in dry CH_2Cl_2 (10 ml) was added 2 equiv of $EtAlCl_2$ under nitrogen at room temperature. The mixture was stirred at room temperature for 12 hours and quenched with sat. $NaHCO_3$. The whole was vigorously stirred for 30 minutes and then $Al(OH)_3$ was filtered off through celite. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The organic layer and the extracts were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel eluting with *n*-hexane:ethyl acetate (10:1 - 5:1) to give an aryl ketone **2** or an aldehyde **3**.



Scheme 1

Table 1 Reactions of 3-Aryl-ß-Sultams with $EtAlCl_2$

Entry	Sultam				Products	
	Compd No.	Ar	R^1	R^2	R^3	(%yields)
1[a)]	**1a**	Ph	H	Ph	Ph	**2a**(56), **1a**(12)
2	**1a**	Ph	H	Ph	Ph	**2a**(81)
3	**1b**	Ph	Ph	H	Ph	**2a**(78)
4[b)]	**1c**	*p*-$MeOC_6H_4$	H	Ph	Ph	**2b**(62), **4**(31)
5	**1d**	*p*-MeC_6H_4	H	Ph	Ph	**2c**(85)
6	**1e**	*p*-MeC_6H_4	Ph	H	Ph	**2c**(85)
7	**1f**	*p*-ClC_6H_4	H	Ph	Ph	**2d**(79)
8	**1g**	*p*-ClC_6H_4	Ph	H	Ph	**2d**(80)
9	**1h**	*p*-$NO_2C_6H_4$	H	Ph	-	complex mixture
10	**1i**	Ph	H	*p*-MeC_6H_4	*p*-MeC_6H_4	**2c**(85)
11	**1j**	Ph	H	*p*-ClC_6H_4	*p*-ClC_6H_4	**2d**(74), **1j**(7)
12	**1k**	Ph	H	2,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_3$	**2e**(70), **1k**(7)
13	**1l**	Ph	H	H	-	N.R.
14	**1m**	*p*-MeC_6H_4	H	H	-	N.R.
15	**1n**	Ph	H	Me	-	N.R.
16	**1o**	Ph	Me	H	Me	**2f**(13), **1o**(61)
17	**1p**	Ph	Et	H	Et	**2g**(19), **1p**(61)
18	**1q**	*p*-MeC_6H_4	H	Me	-	N.R.
19	**1r**	*p*-MeC_6H_4	Me	H	Me	**2h**(35), **1r**(44)
20	**1s**	*p*-ClC_6H_4	Me	H	Me	**2i**(trace), **1s**(76)
21	**1t**	Ph	Me	Me	-	**3a**(73)
22	**1u**	*p*-MeC_6H_4	Me	Me	-	**3b**(78)
23	**1v**	*p*-$MeOC_6H_4$	Me	Me	-	**3c**(89)
24	**1w**	*p*-BrC_6H_4	Me	Me	-	complex mixture

a) 1.1 Equiv of $EtAlCl_2$ was used. b) 2.2 Equiv of $EtAlCl_2$ was used.

Reactions of 3-aryl-ß-sultams **1a-w**[3] bearing a variety of substituents at C-4 with $EtAlCl_2$ provided aryl ketones **2a-i** or aldehydes **3a-c**[4] in the yields shown in Table 1 (Scheme 1). The reactions were influenced by cation stabilizing capability of C-4 substituents and by steric relation between substituents at C-3 and C-4. In the cases of 3-aryl-4-phenyl-ß-sultams **1a-g**, benzophenone derivatives **2a, c, d** were obtained in good yields regardless of the configuration of C-3 and C-4 aryl groups (entries 2,3 and 5, 6 and 7, 8) and of electronic nature of substituents at C-3 phenyl groups (entries 2, 4, 5, 7 and 3, 6, 8, Figure 1, **A**). Reaction of **1h** with a strong electron-attracting *p*-nitro group gave a complex mixture (entry 9). On the other hand, a slight substituent effect was observed in the reactions of 4-aryl-3-phenyl-ß-sultams **1a, i-k** (entries 2, 10-12). An electron-donating *p*-methyl group stabilized a benzylic cation and promoted the C-S bond cleavage, while an electron-withdrawing chloro group retarded it and small amounts of the starting materials **1j** and **1k** were recovered. 4-Non-substituted-ß-sultams **1l-m** did not suffer from the C-S bond cleavage and the starting materials were recovered (entries 13, 14) because the C-4 cations were less stable than those of **1a-k** (Figure 1, **B**). A remarkable substituent effect of C-3 phenyl group was observed in reactions of *trans*-4-alkyl-ß-sultams **1o, p, r, s** (entries 16, 17, 19, 20). The increase of electron density on C-3 aryl groups accelerated the rate of anchimeric assistance to the resulting cation and made it possible to proceed 1,2-aryl rearrangement

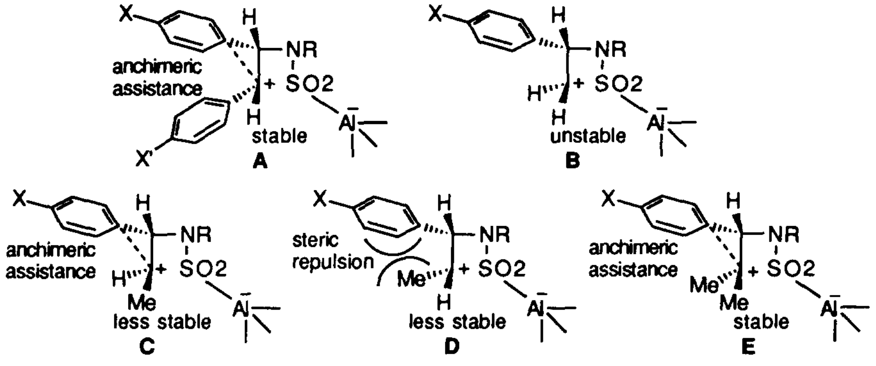
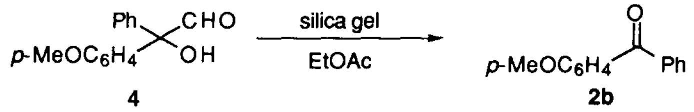


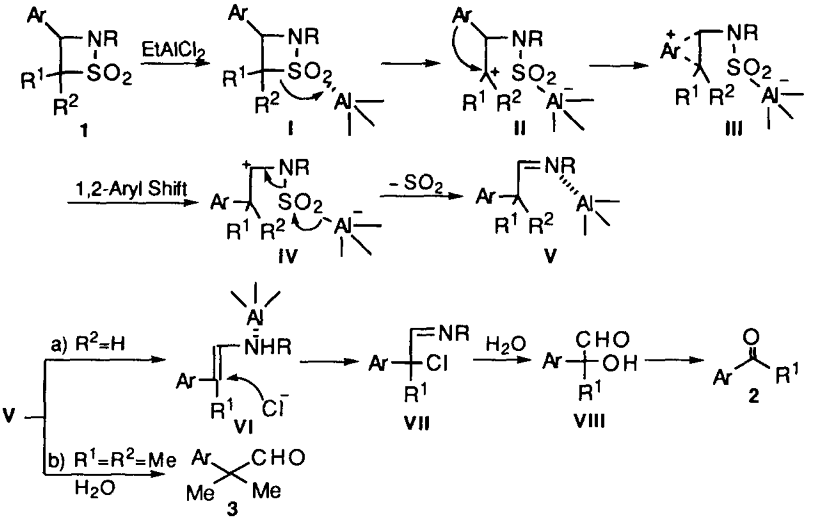
Figure 1

(Figure 1, C). In the cases of *cis*-4-methyl-ß-sultams **1n**, **q**, steric repulsion between aryl and methyl groups prevented anchimeric assistance (Figure 1, **D**), and no aryl ketones were obtained (entries 15, 18). Aldehydes **3a-c** were derived from 4,4-dimethyl-ß-sultams **1t-v** because the C-4 cations generated from **1t-v** were more stable than those from *trans*-4-methyl-ß-sultams enough to bring about C-S bond cleavage (entries 21-24, Figure 1, **E**).

The reaction of **1c** with $EtAlCl_2$ afforded an α-hydroxyaldehyde **4**[5] in 31 % yield together with 4-methoxybenzophenone (**2b**). The hydroxyaldehyde **4** was converted into **2b** by the treatment with silica gel in EtOAc (Scheme 2). This finding indicates that **4** is an intermediate of the benzophenone formation.



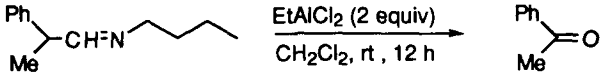
Scheme 2



Scheme 3

A plausible mechanism is proposed as shown in Scheme 3. The C-S bond of a ß-sultam is cleaved by coordination of EtAlCl$_2$ to the sulfonyl group to generate a cationic intermediate **II**. The anchimeric assistance of an aryl group followed by the 1,2-aryl migration provides another carbocation **IV**. An imine **V** is produced by elimination of sulfur dioxide from **IV**. In the case of R^2 = H, **V** isomerizes to an enamine **VI** and coordination of EtAlCl$_2$ enables a chloride ion to attack at the ß-carbon of **VI**. The resulting chloroimine **VII** is hydrolyzed to an aryl ketone **2** *via* an α-hydroxyaldehyde **VIII**. In the case of R^1 = R^2 = Me, an aldehyde is obtained by the hydrolysis of **V**.

In order to confirm that an imine reacts with EtAlCl$_2$ and provides an aryl ketone, we conducted the reaction of *N*-(2-phenylpropylidene)-*n*-butylamine (**5**) with 2 equiv of EtAlCl$_2$ and obtained acetophenone (**2f**) in 63 % yield (Scheme 4).



5

2f (63%)

Scheme 4

In summary, aryl ketones and aldehydes were obtained from 3-aryl-ß-sultams with EtAlCl$_2$. The reactions were influenced by cation stabilizing capability of C-4 substituents, by the electron density of C-3 aryl group and by the steric relation between C-3 and C-4 substituents, and anchimeric assistance played an important role for the selective C-S bond cleavage.

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2. For review: Chanet-Ray, J.; Vessiere, R. *Org. Prep. Proced. Int.*, **18**, 157 (1986).
3. ß-Sultams **1a-s** were prepared by the 2+2 cycloaddition reactions of imines with sulfonyl chloride. *cis*- and *trans*-Isomers were separated by column chromatography on silica gel.; Tsuge, O.; Iwanami, S. *Bull. Chem. Soc. Jpn.*, **43**, 3543 (1970). Methylation of ß-sultams **1l** and **m** with excess LDA and MeI provided 4,4-dimethyl-ß-sultams **1t** and **u**, respectively. In the same manner ß-sultams **1v** and **w** were obtained from the corresponding ß-sultams prepared by the reactions of imines with mesyl chloride.
4. Aryl ketones **2a-i** and aldehydes **3a-c** exhibit physical and spectroscopic properties consistent with their proposed structures.
5. **4**: light yellow oil; ^{1}H NMR (CDCl$_3$) δ: 3.81 (3H, s, OMe), 4.33 (1H, brs, OH), 6.92 (2H, d, J = 8 Hz, ArH), 7.26 (2H, d, J = 8 Hz, ArH), 7.35-7.40 (5H, m, ArH), 9.93 (1H, s, CHO); ^{13}C NMR (CDCl$_3$) δ: 55.3 (q), 83.1 (s), 114.3 (d), 127.4 (d), 128.4 (d), 128.8 (dx2), 131.4 (s), 139.4 (s), 159.7 (s), 198.0 (d); IR (NaCl) cm^{-1}: 3460 (OH), 1720 (C=O); MS (*m/z*): 213 (base, M$^+$-CHO).

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