NOVEL STEREOSELECTIVE SYNTHESIS OF β-LACTAMS VIA EPISULFONIUM ION INTERMEDIATE

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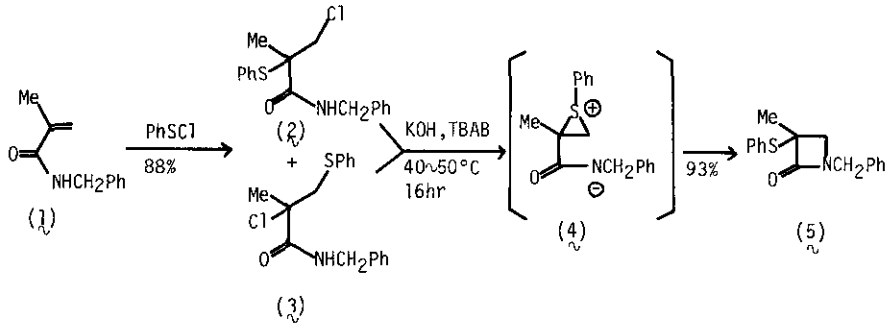
Abstract —— A number of monocyclic β-lactams were synthesised by addition of benzenesulfenyl chloride to α,β-unsaturated olefins followed by base treatment in the presence of a phase transfer catalyst. The cyclization proceeds in a stereoselective manner most probably via an episulfonium ion intermediate.

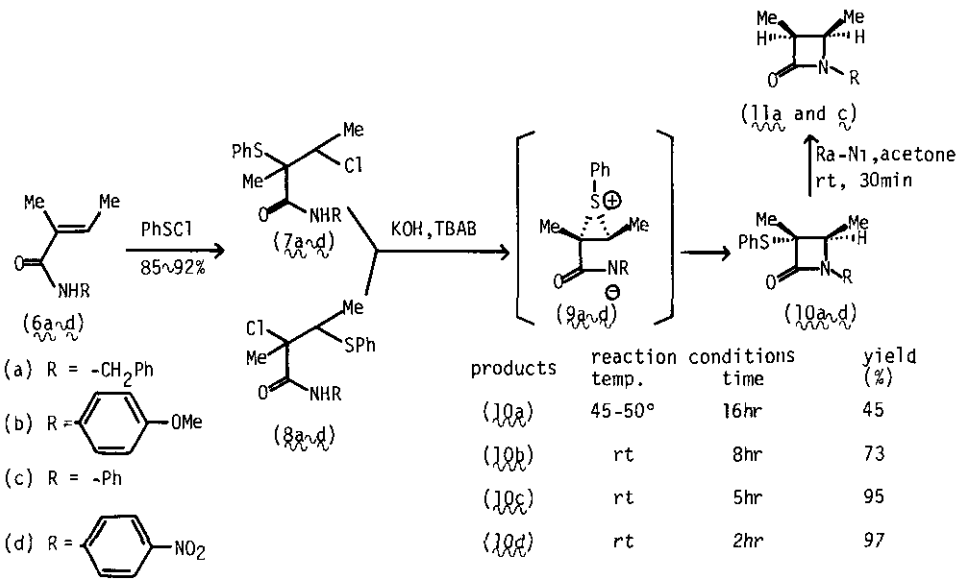
The recent discovery of new types of natural antibiotics possessing monocyclic β-lactam[1], carbapenem[2] and oxapenam[3] structures has promoted considerable synthetic activities in this field. Among a variety of methods for construction of β-lactam ring[4], formation of the N-C_4 bond, which is known as a biomimetic procedure, is one of choice and usually achieved by ring closure of β-haloamides[5,6]. However general synthesis of β-haloamides has not been established and the cyclization is affected to a high degree by rate of addition, concentration of reaction medium and character of halide[7]. We envisaged a β-lactam formation through addition of sulfenyl halides to α,β-unsaturated amides followed by intramolecular substitution anticipating a neighboring effect. Although a reaction between sulfenyl halides and olefins had been well studied[8], there is no report concerned with the addition to α,β-unsaturated amides. We wish to report an efficient and stereoselective synthesis of β-lactams via an episulfonium ion intermediate.

Benzenesulfenyl chloride rapidly reacted with many kinds of α,β-unsaturated amides, forming two regioisomers. The latter were readily prepared from the corresponding acid via the acid chlorides by the usual method. The reaction of methacryl benzylamide (1) with 1.2 molar equivalent of benzenesulfenyl chloride in methylene chloride at room temperature for 2 hr gave in 88 % yield two products in a ratio of 3 : 1. The major product (2)[9] [NMR ($CDCl_3$) δ 1.5 (3H, s, Me), 3.5 and 3.86 (each 1H, each d, J = 11 Hz, CH_2Cl)], the kinetically controlled adduct, was gradually con-

verted to the another one (3)[9] [NMR ($CDCl_3$) δ 1.83 (3H, s, Me), 3.43 and 3.73 (each 1H, each d, J = 14 Hz, CH_2SPh)] by standing it at ambient temperature or by column chromatography on silica gel. The adducts were cyclized by base treatments; the β-lactam formation was effectively conducted with alkalis in the presence of phase transfer catalysts.[5c,d,g] Namely, heating the former (2) (1 mmole) with equivalent mole of potassium hydroxide in the presence of a small amount of tetra-n-butyl-ammonium bromide (TBAB) in a mixture of water (0.2 ml) and benzene (20 ml) at 40 - 50°C for 16 hr furnished the azetidinone (5)[9] [IR ($CHCl_3$) 1745 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.53 (3H, s, Me), 3.03 (2H, br s, C_4-H_2)] in 93 % yield. Interestingly, the regio-isomer (3) also formed 5 in a similar yield on the treatment under the same conditions. By one pot reaction without isolation of the adduct, 5 was obtained in 52 % yield from 1. Purification of the mixture of adducts from the excess of the sulfenyl chloride by a short column chromatography gave usually better results.

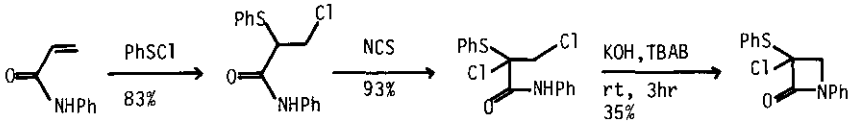


The amides (6a - d) derived from tiglic acid produced two adducts (7a - d)[9] and (8a - d)[9], respectively, by the action of sulfenyl chloride. The slow transformation of the former (7a - d) to the latter (8a - d) was again observed. Single stereoisomer of β-lactams (10a - d)[9] was obtained, respectively, from the mixture of adducts by the treatment with potassium hydroxide in the presence of TBAB. The rate of cyclization was influenced by the acidity of the NH bond; the increased acidity caused the easier formation of β-lactams. The benzenesulfenyl group was easily removed by Raney nickel. The stereochemistry of the azetidinones (11a)[9] and (11c)[9], obtained in 85 and 93 % yield, was determined as cis on the basis of coupling constant (J = 6 - 7 Hz) between two hydrogens on β-lactam ring. The spectral data of the former (11a) were consistent with the reported ones[10]. The above observations strongly suggest that the two adducts (7a - d) and (8a - d) are not stereo-isomers but regio-isomers and the cyclization proceeds via the episulfonium ion intermediate[11] such as (4) and (9a - d).



products	reaction conditions temp.	time	yield (%)
(10a)	45-50°	16hr	45
(10b)	rt	8hr	73
(10c)	rt	5hr	95
(10d)	rt	2hr	97

Base treatments of the adduct (13)[9] prepared from acryl anilide (12), gave no β-lactam but the dehydrochlorinated product. On the reaction of 13 with NCS[12] in carbon tetrachloride at room temperature for 3 hr, the α-chlorinated compound (14)[9] was synthesized in good yield. The cyclization 14 to 15[9] was accomplished by similar reaction conditions as above.



Thus the reaction of benzenesulfenyl chloride and α,β-unsaturated amides provides a versatile route to β-lactams. Application of this methodology to the synthesis of biologically active compounds is now in progress.

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