CLEAVAGE REACTIONS OF PENICILLIN NUCLEI WITH SEYFERTH REAGENTS[1]

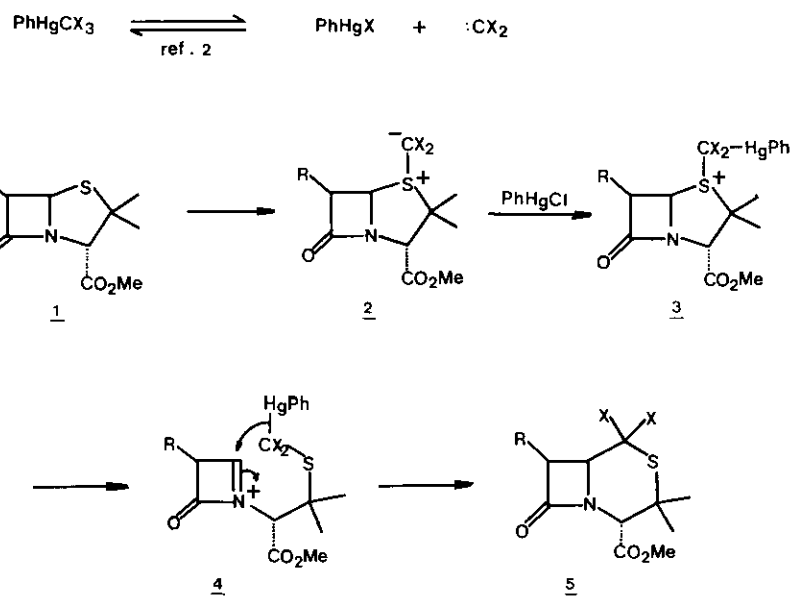
Jahyo Kang*, Weon Bin Im, Soon-gyu Choi, Daesung Lim, Young Ro Choi, Hyung Geun Cho, and Jae Hyoung Lee

Department of Chemistry, Sogang University, Mapoku, Seoul 121-742, Korea

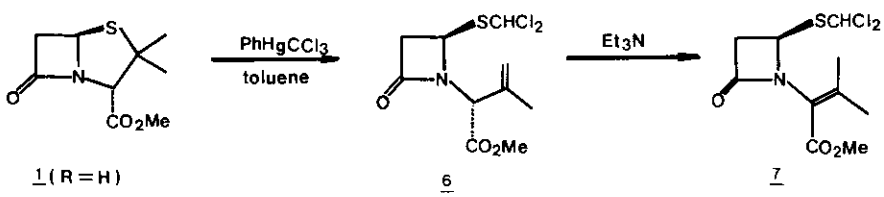
Abstract - Various penams were converted to the corresponding 4-dihalomethylthio-azetidinones by $PhHgCX_3$.

During the course of our attempts to cleave thiazolidine ring of penams with carbon nucleophile with aid of thiaphiles, Seyferth reagents[2], $PhHgCX_3$, were examined as shown in the Scheme I.

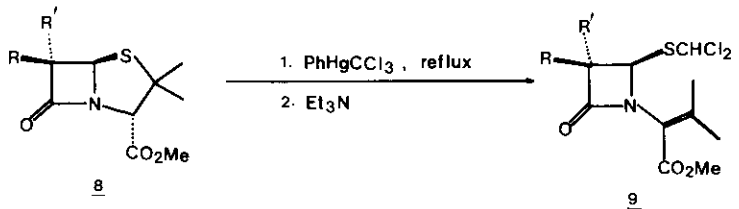
Scheme I



However, upon heating of a mixture of the penam (1; R=H) with $PhHgCCl_3$ in toluene, a β,γ-unsaturated ester 6(R=H) was formed, which was isolated in 48 % yield as an α,β-unsaturated ester 7 after isomerization with Et_3N at room temperature.



To see the generality of the reaction, various penam compounds 8 were individually treated with $PhHgCCl_3$ in refluxing toluene as shown in Table 1. After disappearance of the starting material, Et_3N was added at 23°C to effect isomerization. After aqueous work-up and chromatography, the corresponding α,β-unsaturated esters 9 were isolated in moderate yields (Table 1).



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R	R'	
PhtN–	H	a
	Br	b
H		c
Br	Br	d
Br	H	e
H	H	f
H	Br	g
$PhCH_2CONH$–	H	h
$PhOCH_2CONH$–	H	i

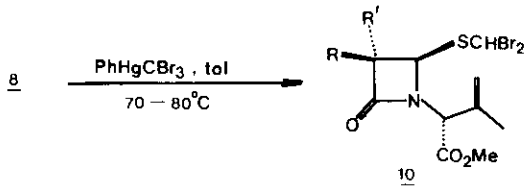
Table 1. Reactions of Penams with $PhHgCCl_3$.

Substrate	Ring Cleavage[a]			Isomerization[b]		Product (Yield,%)[c]
	$PhHgCCl_3$(eq.)	Solvent	h	Et_3N(eq.)	h	
8a	3.0	tol[d]	3.0	0.5	1.0	9a (94%)
8b	2.5	tol[d]	2.5	0.5	1.0	9b (79%)
8c	2.0	tol[d]	1.0	0.5	1.0	9c (58%)
8d	6.0	tol[d]	3.0	1.0	1.0	9d (49%)
8e	3.0	tol[d]	1.0	0.5	1.0	9e (49%)
8f	2.5	tol[d]	1.0	0.5	1.0	9f (48%)
8g	4.0	tol[d]	6.0	0.5	1.0	9g (41%)
	3.0	PhH[e]	24.0	0.5	1.0	9g (45%)

[a] Reaction in refluxing solvent. [b] At 23°C. [c] Isolated pure compound.
[d] Toluene. [e] Benzene.

As can be seen in Table 1, penams of various type could be subjected to the present reactions, but with two exceptions having relatively acidic protons. Thus, methyl esters of Penicillin G and V, 8h and 8i, gave complex mixtures.

Since $PhHgCBr_3$ gives $:CBr_2$ under milder condition[2], reactions with $PhHgCBr_3$ were investigated. As anticipated, ring cleavage could be effected under mild conditions to give the corresponding dibromomethyl compounds 10 (Table 2).



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However, the dibromopenam 8d gave the corresponding α,β-unsaturated compound 11 even without base treatment, for which the reasons are not clear at this moment.

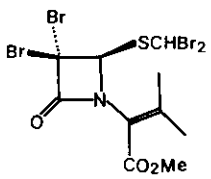

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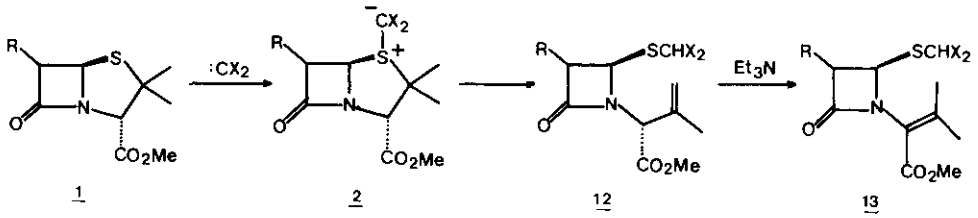
Table 2. Reactions of Penams with $PhHgCBr_3$

Substrate	Ring Cleavage			Product (Yield,%)[a]
	$PhHgCBr_3$(eq.)	Solvent (Temp)	h	
8c	1.5	tol[b] (80°C)	4	10c (69%)
8d	1.5	PhH[c] (80°C)	3	11 (69%)
8f	2.0	tol[b] (80°C)	3	10d (68%)[d]

[a] For pure product. [b] Toluene. [c] Benzene. [d] Based on the unrecovered starting material. Normal yield was 64%.

Considering the results obtained so far, the mechanism should involve free carbenes, which undergo addition to the sulfur atom in penams 1. But without intervention of mercury electrophiles, the resulting sulfur ylide 2 undergoes 1,2-bond cleavage to form a β,γ-unsaturated ester 12 (Scheme II). Precedents to this reaction exist in a number of cases, where penams were treated with diazoalkanes in the presence of a catalyst such as rhodium acetate.[3] However, introduction of α,α-difunctional methyl groups in the products, 12 and 13, offer many opportunities for further elaboration. Details will be reported in the forthcoming publications.

Scheme II



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