# A SIMPLE METHOD FOR THE PREPARATION OF CIS-(3-AZIDO-4-STYRYL)-2-AZETIDINONE

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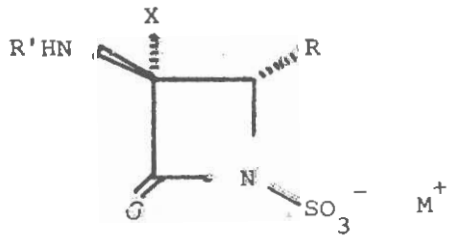
## ABSTRACT

The synthesis of the title compound is described. Deprotection of cis(N-trityl-3-azido-4-styryl)- 2-azetidinone to cis-(3-azido-4-styryl)- 2-azetidinone was found to be accelerated by the special salt effect under acidic condition.

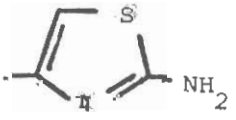
## INTRODUCTION

Agrobacterium radiobacter produces a mixture of monocyclic β-lactam possessing the general structure I, having weak antibacterial activity against a number of pathogenic microorganisms[1-3]. The methoxylated monobactams Ia show a high degree of stability to hydrolysis by β -lactamases, whereas the non-methoxylated compound Ib is susceptible to enzyme hydrolysis[4].

We have recently reported[5] the synthesis of a series of 4-substituted monobactamic acids(i.e. Ic) having stability toward β-lactamases. This was consistent with the biological activity and β-lactamases stability of aztreonam Id[4]in which the α-methyl group at 4-position of aztreonam increases the antibacterial activity of this compound as well as its stability toward the β-lactamases[4].




Ia, X=OMe, R=H , R'=$COCH_2ph$
Ib, X=H , R=H , R'=$COCH_2ph$
Ic, X=H , R=styryl, R'=$COCH_2ph$
Id, X=H , R=Me
R'=$COC(=NOCMe_2CO_2H)$.



Since the preparation of the 4 - substituted monobactamic acid precursor is a tedious task, in this article the high yield synthesis of cis-( 3- azido-4-styryl)-2- azetidinone (7) was undertaken. Furtheremore, the key intermediate 7 can easily be converted to a series of the naturally occuring β-lactam antibiotics having penicillin or cephalosporin nucleus. The method used to prepare 7 was based on that initiated and developed by ourselves[6-13].

## EXPERIMENTAL

General: Reagent - grade solvents were distilled first and then stored over molecular sieves (type 4 A°). t-butyl amine, trityl chloride, mono - methoxytrityl chloride, dimethoxytrityl chloride, and cinnamaldehyde were purchased from Merck Chemical company. Column chromatography: short column of silica gel 60 Merck (230 - 400 mesh) were packed in glass columns ( ϕ 2 or 3 cm) using 15-30 g of silica gel per g of crude mixture. TLC: Merck silica gel 60 F 254 analytical sheets. M.P. Buchi 510, uncorrected. IR spectra: Beckman IR 8 spectrophotometer. $^1$H-NMR spectra: Hitachi R-248 spectrophotometer.

General procedure for the preparation of trityl amines 4a-c .

Representative procedure: trityl chloride (3a, 0.1 mol) was dissolved in $CH_3CN$ (400 ml). Ammonia gas was bubbled into the solution for 15 min. Filteration and evaporation gave trityl amine (4a, 98%) as an oil. IR($CH_2Cl_2$): 3200- 3400 ($NH_2$). $^1$H-NMR($CDCl_3$): 3.48 (br., 2H, $NH_2$, exchanged with $D_2O$); 7.18 (s, 15H , 3Ph).

4b: Oil (98%). IR($CH_2Cl_2$): 3200 - 3400 ($NH_2$), 1110 (ether). $^1$H-NMR ($CDCl_3$): 3.50 (br., 2H, $NH_2$, exchanged with $D_2O$); 3.78 (s, 3H, $CH_3$); 6.79 - 7.63 (dd, 4H, J=8, 20 Hz, PhOMe); 7.20 (s , 1 OH, 2Ph).

4c: Oil (98%). IR($CH_2Cl_2$): 3200 - 3410 ($NH_2$), 1120 (ether). $^1$H - NMR ($CDCl_3$): 3.45 (br., 2H, $NH_2$, exchanged with $D_2O$); 3.75 (s, 6H, $2CH_3$); 6.80- 7.60 (dd, 8H, J=8, 20Hz, 2PhOMe); 7.19 (s, 5H, Ph).

General method for the synthesis of β-lactams 2 and 6a-c .

Representative procedure: to t-butyl amine (1, 0.02 mol) in 300 ml dry benzene was added cinnamaldehyde (0.01 mol). The solution was refluxed for 6 h using a Dean Stark trap to remove the $H_2O$ formed. Evaporation of the benzene afforded the corresponding Schiff base in quantitiative yield. This was used without purification for the next step. To a solution of the crude Schiff base (0.01 mol) and $NEt_3$ ( 0.02 mol) in 200 ml dry $CH_2Cl_2$ at reflux temperature was added azidoacetyl

chloride(0.01 mol)in 20 ml dry $CH_2Cl_2$ dropwise over a period of 1 h. After the addition was complete,the stirred solution was refluxed for an additional 5 h.The solution was then washed with $H_2O$ (100ml x 3).The organic layer was dried($Na_2SO_4$), filtered , and evaporated.The crude product( brown oil)was treated with active charcoal (neutral)in 120 ml of anhydrous ether, filtered and evaporated to give a yellow oil.Chromatography on silica gel and elution with $CH_2Cl_2$ afforded β-lactam 2(90%)as an oil.IR($CH_2Cl_2$): 1770( β-lactam).$^1$H-NMR($CDCl_3$): 0.96 (s,9H,t-Bu);4.31-4.89(m,2H,CHCHCl) ; 6.17(dd,1H,$J_1$=16 Hz,$J_2$=7 Hz,PhC=CH); 6.61(d,1H,J=16 Hz,PhCH=C);7.25(s,5H, Ph).

β-lactams 6a-c were similary prepared,as oil,from Schiff bases 5a-c which,in turn,were prepared from trityl amines 4a-c in the same manner which was described above.

6a:IR($CH_2Cl_2$):2100($N_3$),1775( β-lactam).$^1$H-NMR($CDCl_3$):4.30-4.61(m,1H, H-C(4));4.80(d,1H,J=5 Hz ,H-C(3)) ; 5.79-6.11(m,2H,CH=CH);7.21(br.,s, 20 H,4Ph).

6b:IR($CH_2Cl_2$):2100($N_3$),1772( β-lactam).$^1$H-NMR($CDCl_3$):3.65(s,3H,$CH_3$); 4.21-4.52(m,1H,H-C(4));4.75(d,1H,J= 5 Hz,H-C(3));5.79-5.95(m,2H,CH=CH) ; 6.11-7.19(dd,4H,J=9,22Hz,PhOMe);7.21 (s,15H,3Ph).

6c:IR($CH_2Cl_2$):2100($N_3$),1775( β-lactam).$^1$H-NMR($CDCl_3$):3.67( 2s,6H , $CH_3$);4.25-4.53(m,1H,H-C(4));4.75(d , 1H,J=5 Hz,H-C(3));5.80-5.98(m,2H,CH = CH);6.15-7.20(dd,8H,J=9.21Hz,2PhOMe) , 7.24(s,10 H,2Ph).

General procedure for detritylation of β-lactams 6a-c to cis-( 3 -azido-4-styryl)-2-azetidinone(7).

All compounds 6a-c were converted to 7 by an identical procedure. The following is a reprsentative procedure: β-lactam 6b (0.01 mol)was dissolved in $CF_3COOH$(30 ml).A trace amount of $KClO_4$ was added and the solution stirred at 25°C for 1h.Evaporation and purification on silica gel using $CHCl_3$ as solvent gave 7 (100%)as a foam.IR($CH_2Cl_2$):2100($N_3$), 1762( β-lactam).$^1$H-NMR($CDCl_3$):4.30-4.53(dd,1H,$J_1$=5 Hz,$J_2$=7 Hz,H-C(4)) ; 4.78(d,1H,J=5 Hz,H-C(3));6.15(dd,1H, $J_1$=16Hz,$J_2$=7 Hz,PhC=CH);6.68(d,1H , J=16 Hz,PhCH=C);6.70(br.,1H,NH);7.31 (s,5H,Ph).

## RESULTS AND DISCUSSION

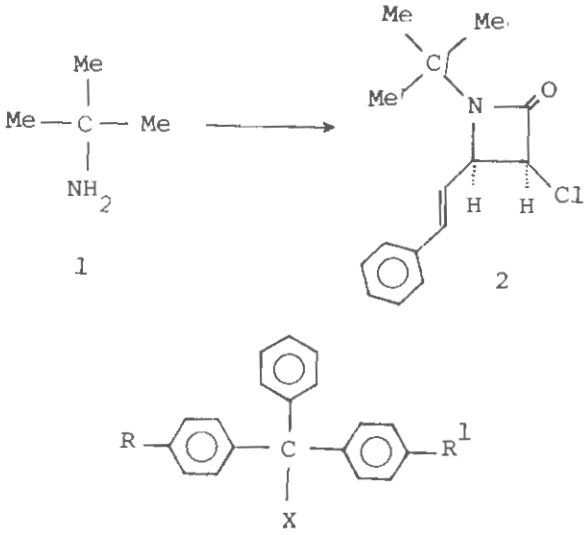
As a model,the readily available t-butylamine (1) was reacted with cinnamaldehyde. The corresponding Schiff base upon treatment with chloroacetyl chloride gave β-lactam 2. The expected cis-configuration of 2 was confirmed by $^1$H-NMR,which showed a characteristic coupling constant of 5 Hz for β-lactam protons[14,15].All attempts to remove the t-butyl group from the β-lactam nitrogen failed

(i.e.$CF_3COOH$) and resulted in recovery or destruction of the starting material. Since the t-butyl group is an acid labile group, the failure in deprotection of the azetidinone function has to be due to the special stereochemistry of the lone pair electrons of the nitrogen atom which is not coplanar with the carbonyl function of the β-lactam ring. This could prevent the ease of the deprotection of the nitrogen atom in compound 2 through a carbocation formation.

At this stage in the development of a general procedure for the synthesis of monobactams, it became essential to examine the effect of the more acid labile groups. In terms of deprotection of the azetidinone function we wished to take advantage of the 10-fold reduction in time required to remove a dimethoxytrityl group compared to a monomethoxytrityl group[16].

Trityl chlorides 3a-c were chosen as the starting materials. Treatments with $NH_3/CH_3CN$ gave the corresponding trityl amines 4a-c in excellent yields. Separate reactions with cinnamaldehyde in boiling benzene afforded the respective Schiff bases 5a-c, which upon reactions with azidoacetyl chloride and $NEt_3$ in $CH_2Cl_2$ at boiling temperature gave the corresponding β-lactams 6a-c in about 60% yield based on(4). Deprotection of the trityl groups from 6a-c to afford the desired compound (7) was achieved by $CF_3COOH$ at 25°C after 24 h. In fact deprotections of the trityl functions from the nitrogen atom of the β-lactam ring were found to be more difficult than the respective deprotection of the trityl groups from ordinary amides, amines, ethers, and esters[17]. The unusual difficulties in deprotection of the trityl functions from the azetidinones must be due to the spatial arrangement of the lone pair electrons of the nitrogen atom of the β-lactam ring. Furthermore, it is of interest to note that there was not much reduction in time required to remove dimethoxytrityl group compared to that of the monomethoxytrityl group. However, we have found that the addition of a trace of $KClO_4$ accellerated the rate of deprotection reaction of the trityl function from 24h to 1h. This is due to the special salt effect which causes the rate of ionization of the trityl function to be equal to the rate of the product formation[18]. The reactions are outlined in scheme 1 & 2 and the results are collected in table 1.

It should be noted that detritylation of an ordinary amide function or other compounds such as amines or ethers did occur within 10 second using 1% benzenesulfonic acid (BSA) at 25°C [19].

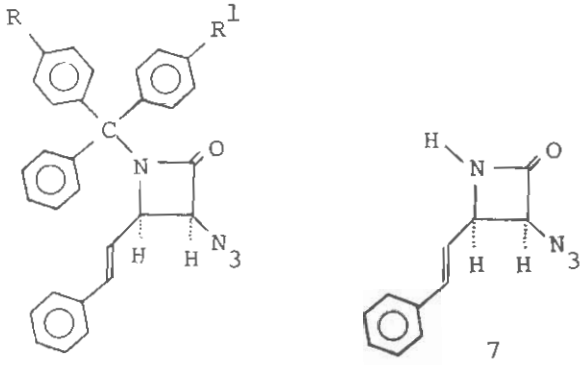


1 2



3a,R=H ,$R^1$=H ,X=Cl
b,R=H ,$R^1$=OMe,X=Cl
c,R=OMe,$R^1$=OMe,X=Cl
4a,R=H ,$R^1$=H ,X=$NH_2$
b,R=H ,$R^1$=OMe,X=$NH_2$
c,R=OMe,$R^1$=OMe,X=$NH_2$
5a,R=H ,$R^1$=H ,X=N=$(CH)_2$=CHPh
b,R=H ,$R^1$=OMe,X=N=$(CH)_2$=CHPh
c,R=OMe,$R^1$=OMe,X=N=$(CH)_2$=CHPh

Scheme 1



6a,R=H ,$R^1$=H
b,R=H ,$R^1$=OMe
c,R=OMe,$R^1$=OMe

Scheme 2

Table 1-Deprotection of azetidinones

| compound | condition | time(h) | product(%) |
|---|---|---|---|
| 2 | $CF_3CO_2H/KClO_4$ | 100 | 7 (0) |
| 6a | $CF_3CO_2H$ | 24 | 7 (50) |
| 6a | $CF_3CO_2H/KClO_4$ | 2.5 | 7 (85) |
| 6b | $CF_3CO_2H$ | 24 | 7 (80) |
| 6b | $CF_2CO_2H/KClO_4$ | 1 | 7 (100) |
| 6b | $CF_3CO_2H/CH_3CN$(1:1) | 72 | 7 (35) |
| 6b | $CF_3CO_2H/CH_2Cl_2$(1:1) | 72 | 7 (20) |
| 6b | $BSA/CH_3CN$(3%) | 100 | 7 (1) |
| 6c | $CF_3CO_2H$ | 24 | 7 (83) |
| 6c | $CF_3CO_2H/KClO_4$ | 1 | 7 (100) |

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