SYNTHESIS OF 4-SUBSTITUTED 2-AZETIDINONES

by

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ABSTRACT

4-Substituted 2-azetidinones can be obtained in excellent yields from the reactions of various cuprates with 4-acetoxy-2-azetidinone. When 4-acetoxy-2-azetidinone was treated with one equivalent of the cuprates in ether: dimethylsulfide (1:1) at -50°C to -30°C, only 20-30% of the corresponding 4-substituted 2-azetidinones were obtained. However when two equivalents of the cuprates were used, the yields were excellent (71-98%). By this method we have been able to introduce alkyl, aryl, allyl and alkenyl groups at the 4-position of 2-azetidinones in excellent yields.

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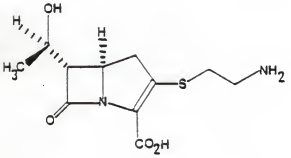
I. INTRODUCTION

The discovery of thienamycin (1)[1], an unusually potent carbapenem antibiotic, has led to intense activity in the synthesis of β-lactam antibiotics. These substances possess a reactive β-lactam linkage, which show high antibacterial potency and a wide antibacterial spectrum. The β-lactam linkage is also known to be present in Penicillins (2)[2] and other related antibiotics.



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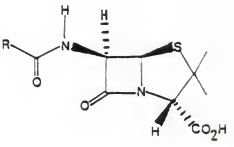

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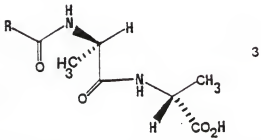
However, unlike the penicillins which have a carbon-sulfur bond at C-4, the carbapenems have a carbon-carbon bond at the 4-position . Although the penicillins have been known for quite some time, the carbapenems have been extensively studied only in the last 10 years. The chemistry of carbapenems gained momentum in 1976, following the isolation of thienamycin from a Streptomyces species.

Thienamycin has unusually high potency against both gram-positive and gram-negative bacteria. Of particular interest is its activity against Pseudomonas spp. and its resistance to bacterial β-lactamase[3].

The mode of action of these β-lactam antibiotics is still not clear. It has been proposed that a β-lactam antibiotic inhibits transpeptidase activity because it is a structural analogue of the D-alanyl-D-alanine portion of the nascent peptidoglycan [6].



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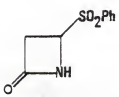
However, thienamycin lacks the β-amide functionality present in penicillins and other related antibiotics. Possibly the hydroxyl group in thienamycin can bind the same site normally bound by the β-amido group of other β-lactam antibiotics when complexing with the bacterial cell wall enzymes.

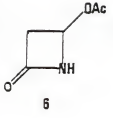
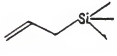
The most common methods for preparing penicillins and their derivatives are still by direct fermentation or by synthetic modification of fermentation derived starting materials. However, the low yields[4] obtained for the carbapenems by fermentation processes have engendered intense interest in synthetic approaches to these biologically important compounds, particularly the construction of the unusual ring system.

II. BACKGROUND

Since the discovery of thienamycin and other related carbapenem antibiotics, much attention has been focused on carbon-carbon bond formation at the 4-position of 2-azetidinones. The formation of a carbon-carbon bond at the C-4 position of a β-lactam might be very useful in the synthesis of carbapenem type antibiotics. Although many 2-azetidinones bearing carbon substituents at C-4 are known, there have been few reports of carbon-carbon bond formation at C-4. In all these reports either 4-phenylsulphonyl-azetidin-2-one (5) or 4-acetoxyazetidin-2-one (6) have been used as starting materials[5]. Table I summarizes all the methods for carbon-carbon bond formation at C-4 that have been reported so far.

TABLE–I

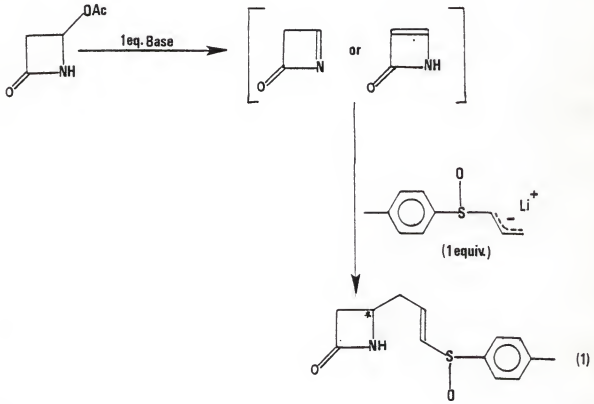
STARTING MATERIAL	REAGENT	 % yield	REFERENCE NO.
	$LiCu(Bu^n)_2$	R : Bu^n, 94	7
 5	EtMgBr	R : Et , 74·2	7
	$CH_2{=}CHMgBr$	R : $CH{=}CH_2$, 65·5	7
	$LiCu(CH_2{-}CH{=}CH_2)_2$	R : $CH_2{-}CH{=}CH_2$, 100	7

$LiCu(Bu^n)_2$	R : Bu^n , 89	7
EtMgBr	R : Et , 12·4	7
 6	$CH_2{=}CHMgBr$ R : $CH{=}CH_2$, 3·5	7
n-BuLi	R : Bu^n, 12	8
 R : Bz or t-Bu	 R : Bz , 96 R : t-Bu , 80	9
	R : $CH_2{-}CH{=}CH_2$, 63	10

As seen from the table, only a few cases for carbon-carbon bond formation using 4-phenylsulphonylazetidin-2-one(5) as the starting material have been reported and in all cases the yields are reasonably good. This starting material 4-phenylsulphonylazetidin-2-one(5) has to be prepared from 4-acetoxyazetidin-2-one(6). However, if 4-acetoxyazetidin-2-one(6) is used

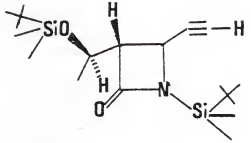
as the starting material, the yields in many cases are low. We therefore investigated the possibility of improving the yield for carbon-carbon bond formation at the 4-position of β-lactam by using 4-acetoxyazetidin-2-one(6) as the starting material.

Since we have been successful in our laboratory for obtaining good asymmetric induction in enones by reacting them with chiral allylsulfinyl anion, it was tempting for us to see whether β-lactam can be used as the substrate. A possible way to achieve this, is to react the azetidinone 6 with one equivalent of base and one equivalent of chiral allylsulfinyl anion as shown in equation 1.



(1)

In a recent communication[11], the preparation of β-lactam 4 a key intermediate in the asymmetric synthesis of (+)-thienamycin has been reported.



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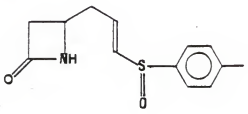
A key step in the synthesis of β-lactam 4 was the stereoselective phenylthiolation at the 4-position of either of the two starting materials 5 or 6 with thiophenol in benzene containing cinchonidine at 35° for 62.5 hrs. The product (+)-4-phenylthioazetidin-2-one (18) was obtained in 96 and 79% yield and 54 and 38% optical purity respectively.

III. RESULTS AND DISCUSSION

Before studying the reaction of azetidinone 6 with chiral allylsulfoxide, we decided to initially investigate the reaction of racemic allylsulfoxide with azetidinone 6.

When azetidinone 6 is allowed to react with one equivalent of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C and one equivalent of racemic allylsulfinyl anion [formed by treating one equivalent of racemic p-tolylallylsulfoxide with one equivalent of lithium diisopropylamide in tetrahydrofuran (-78°C - -30°C)], only a trace amount of the desired compound 7 was obtained.

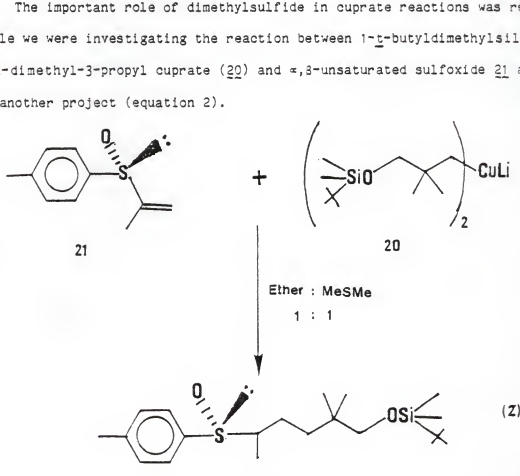


7

The NMR spectrum indicated the presence of unidentifiable polymer in major amount. However, when one equivalent of azetidinone 6 in tetrahydrofuran (-78°C) is allowed to react directly with two equivalents of racemic allylsulfinyl anion in tetrahydrofuran (-78°C - -50°C), about 14% of the desired β-lactam 7 is obtained. Cyclization of the β-lactam 7 would give us a two step synthesis of the carbapenem skeleton. Further, if the azetidinone 6 was allowed to react with two equivalents of chiral p-tolyl allylsulfinyl anion, we would expect the resulting β-lactam to have a chiral center at the 4-position. This β-lactam can next be cyclized to give us a two step asymmetric synthesis of the carbapenem skeleton. As the yield of the β-lactam 7 was low, our main objective was to develop a useful method for

carbon-carbon bond formation at the 4-position of azetidinone 6 and the subsequent cyclization to carbapenem which will serve as synthetic intermediate for the synthesis of thienamycin.

The important role of dimethylsulfide in cuprate reactions was realized while we were investigating the reaction between 1-t-butyldimethylsilyloxy-2,2-dimethyl-3-propyl cuprate (20) and α,β-unsaturated sulfoxide 21 as part of another project (equation 2).



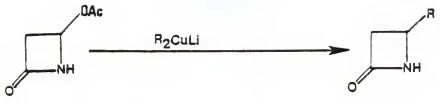
In ether alone the yield of the 1,4-adduct 22 was low but if ether : MeSMe (1:1) was used as the solvent system, about 95% yield of the 1,4-adduct 22 was obtained. Hence dimethylsulfide was playing an important role in cuprate reactions. The literature[7] does mention a few examples in which 4-substituted azetidinones have been obtained by reacting azetidinone 5 or 6 with alkylcuprates. However, in all these reports experimental details such as the solvent used have not been mentioned. This prompted us to investigate the possibility of obtaining 4-substituted azetidinones, by

reacting azetidinone 6 with various cuprates in ether : MeSMe (1:1) as the solvent system.

When azetidinone 6 was treated with one equivalent of the cuprates in ether: dimethylsulfide (1:1) at -50°C - -30°C only 20 - 30% yields of the corresponding 4-substituted-2-azetidinones were obtained (equation 3). However, if two equivalents of the cuprates were used, excellent yields (71 - 98%) were achieved. The results are summarized in Table II.

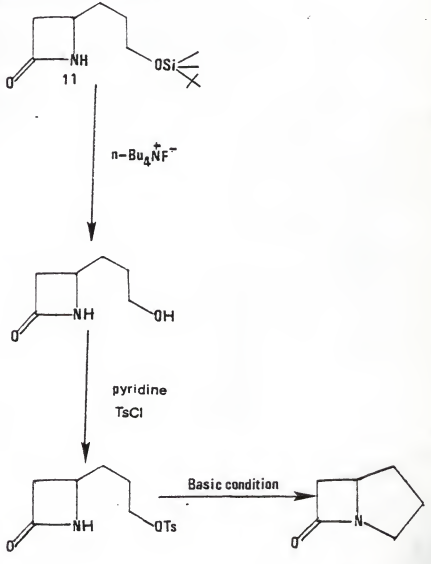
TABLE II REACTIONS OF 4-ACETOXY-2-AZETIDINONE (1) WITH HOMOCUPRATES.

ENTRY	$R_2Cu^-M^+$ R	M	 ISOLATED YIELD (%)
1	$CH_3CH_2CH_2CH_2-$	Li	8 (94)
2	$CH_3CH_2\underset{CH_3}{CH}-$	Li	9 (96)
3	$CH_2=\underset{CH_3}{\overset{CH_3}{C}}-$	Li	10 (90)
4	$\overset{\geq}{\underset{\times}{}}SiOCH_2CH_2CH_2-$	Li	11 (98)
5		MgBr	12 (92)
6	$CH_2=CH-$	Li	13 (75)
7		Li	14 (95)
8		Li	15 (82)
9		Li	16 (80)
10	$CH_2=CHCH_2-$	Li	17 (72)



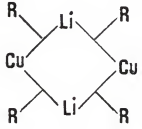
(3)

We have also investigated the possibility of obtaining carbapenem 23 from β-lactam 11. To achieve this, the β-lactam 11 was subjected to the following sequence of reactions indicated below.



The intramolecular cyclization step (23a → 23) is being studied. This thesis will not cover the studies of the cyclization to carbapenem.

The structure of cuprates such as lithium dimethylcuprate and lithium dibutylcuprate has been investigated in ether as a solvent.[12,13] There is much evidence to show that these cuprates possess a dimeric cyclic structure in ether.



R : Me or Bu

It is possible that other dialkylcuprates have a similar cyclic structure.

We are still not sure about the exact mechanism of these cuprate reactions. The mechanisms indicated below account for the improvement in yield caused by using two equivalents of cuprate. However, it is possible that the reaction is proceeding via an entirely different mechanism.

Mechanisms

(a) Since two equivalents of cuprate are required to improve the yield, it is possible that one equivalent of cuprate removes the acidic N-H proton while the second equivalent of cuprate is utilized in displacing the acetate group before elimination takes place.

(b) In this mechanism also, the first equivalent of the cuprate is utilized in removing the acidic N-H proton. However, this mechanism differs from mechanism 'a' in that elimination of the acetate group takes place as soon as the N-H proton is removed resulting in the formation of unstable

cyclic iminone 25. The second equivalent of cuprate now adds across the C=N bond of the iminone.

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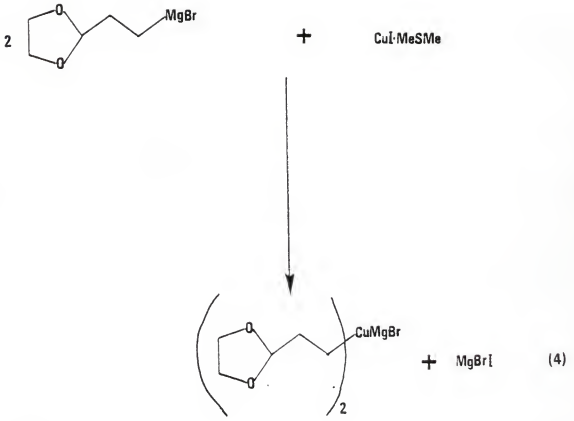
If one equivalent of cuprate is used, then after removing the acidic .. N-H proton, enough cuprate is not available to undergo displacement or addition. Consequently the yield is also low.

(c) Although mechanisms (a) and (b) satisfactorily account for the experimental observation, the possibility that the two equivalents of cuprate complex with the nitrogen of the azetidinone 6 because of the strong affinity of copper for nitrogen cannot be ruled out. This could be followed by some internal displacement of the acetoxy gorup by alkyl group to give the desired β-lactam.

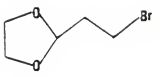
Neither ether nor tetrahydrofuran alone as the solvent in the reaction of 6 with cuprates gave appreciable amount of the desired product. However, the yields are found to improve considerably if ether and dimethylsulfide in 1:1 proportion is used as the solvent system. Therefore dimethylsulfide might be playing an important role in the displacement reaction.

Except for dialkylcuprate (entry 5) which was made from alkylmagnesium bromide and CuI·MeSMe (equation 4), the other cuprates were generated from their corresponding lithium salts as shown in equation 5.



Unlike the dialkylcuprate, divinylcuprate generated from vinylmagnesium bromide gave low yield of β-lactam 13. However, if divinylcuprate was generated from vinyllithium the yield of 13 improved considerably. Further if the vinyllithium was prepared from tetravinyltin and phenyllithium (equation 6),[14] then the divinylcuprate generated as shown in equation 5 did not give any product when reacted with azetidinone 6.

Although most of the byproduct tetraphenyltin was removed prior to the reaction with CuI·MeSMe, it is possible that traces of tetraphenyltin remaining behind interfered in the reaction. Hence an alternative method for the preparation of vinyllithium had to be sought. Vinyllithium was conveniently prepared in ether by allowing vinylbromide to react with 1.2 equivalents of t-butyllithium (1.8 M). This vinyllithium was standardized by titration with diphenylacetic acid dissolved in tetrahydrofuran. The divinylcuprate generated from this standardized vinyllithium when allowed to react with azetidinone 6 gave 75% yield of the β-lactam 13. The spectral data indicated the absence of 4-t-butylazetidin-2-one 10. Therefore all the t-butyllithium must have been used up in the preparation of vinyllithium. Unlike vinyllithium which cannot be prepared from vinylchloride or bromide and ordinary lithium metal,[15] 1-lithiocyclohexene could be generated from 1-bromocyclohexene and lithium metal. The cuprate generated from this 1-lithiocyclohexene when reacted with azetidinone 6 gave excellent yield of the β-lactam 14 (Entry 7). Although 2-(2-bromoethyl)-1,3-dioxolane(12) reacted with magnesium metal in tetrahydrofuran to form the Grignard reagent[16], it did not react with ordinary lithium metal.



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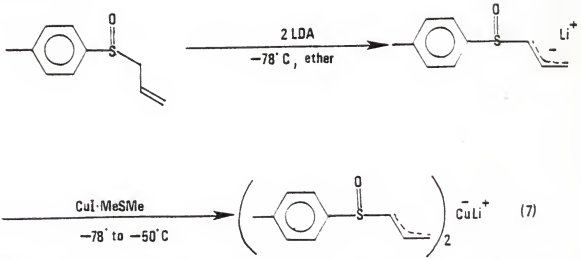
The dialkylcuprate was therefore generated from the corresponding Grignard reagent (Entry 5). This cuprate when allowed to react with azetidinone 6 gave a 92% yield of the desired β-lactam 12.

Since the yields of these cuprate reactions are excellent, it was tempting for us to see if we could improve the yield of 7 by treating azetidinone 6 with two equivalents of racemic p-tolylallyl sulfoxide cuprate. To form the cuprate, racemic p-tolylallyl sulfoxide (2 equivalents) in ether at -78°C was treated with two equivalents of lithium diisopropylamide in ether at -78°C and one equivalent of CuI·MeSMe as shown in equation 7.



(7)

However, unidentifiable polymer resulted on reaction with azetidinone 6.

IV. CONCLUSION

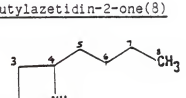
Since the reaction of racemic p-tolylallylsulfoxide with azetidinone 6 did not give good yield, asymmetric induction at C-4 of azetidinone 6 using chiral p-tolylallylsulfoxide was not studied. However, we have been successful in obtaining a very elegant method for the introduction of alkyl, aryl, alkenyl or allyl group at the 4-position of 2-azetidinone. The formation of a carbon-carbon bond at the C-4 position of a β-lactam might be very useful in the synthesis of carbapenem type antibiotics.

V. EXPERIMENTAL

General - Flash chromatography was carried out using E. Merck silica gel 60 (230 - 400 mesh). Infrared spectra (IR) were recorded on a Perkin-Elmer 1330 spectrophotometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were obtained on a Bruker WM-400 (400 MHz for proton and 100 MHz for carbon). Mass spectra (MS) were recorded on a Finnigan automated gas chromatograph EI-CI mass spectrometer.

4-Acetoxy-2-azetidinone (6) was prepared by following the reported method.[5]

1. Preparation of 4-n-butylazetidin-2-one(8)



8

To a stirred mixture of 1·2625g (5 mmoles) of CuI·MeSMe[17] in 20 ml of ether under argon at -20°C was added 6.25 ml (10 mmoles) of nBuLi(1.6M). The reaction solution was stirred at -20°C for 15 mins. and then 20 ml of dimethylsulfide was added. This cuprate solution was cooled to -50°C and a solution of 0.645g (5 mmol) of azetidinone 6 in 6 ml of ether was added. The resulting brownish red solution was stirred at -50°C for 1 hr., poured into a mixture of 80 ml of satd. NH_4Cl and 20 ml of conc. NH_4OH, stirred for 10 mins. and extracted three times with ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (230 - 400 mesh; CH_2Cl_2 : acetone as eluent) to give 0.571g (94% yield) of 8.

Mass Spectra* + (CI, 70eV, 80°C) 128 (M + 1, 100%); (EI, 70eV, 45°C) 128 (M + 1, 47%), 117 (3%), 110 (5%), 84 (M-C_3H_7, 62%), 69 (M-C_4H_{10}, 49%), 56 (M-C_3H_5NO, 100%).

IR(neat)ν_{cms}^{-1} + 3250 (s, broad, N-H stretch) 2900 (s, C-H stretch), 1725 (s,C=O stretch), 1460 (m), 1415 (w), 1370 (m), 1180 (s), 1075 (m), 965 (s), 900 (m).

^{1}H NMR ($CDCl_3$)δ* + 6.13 (broad peak, 1H, N-H),3.58 - 3.63 (m, 1H, C-4H), 3.05 (d,d,d, C-3H, J = 2.2, 5, 14.7 Hz), 2.56 (d,d,d, C-3H, J = 1.3, 2.2, 14.7 Hz), 1.57 - 1.78 (m, 2H, CH_2), 1.24 - 1.41 (m, 4H, $2CH_2$), 0.92 (t, 3H, CH_3, J = 7Hz).

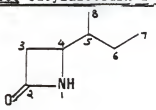
^{13}C NMR ($CDCl_3$)δ* + 168.6 (s, C=O), 47.9 (d, C-4), 43.1 (t, C-3), 34.9 (t, C-5), 28.1 (t, C-6), 22.2 (t, C-7), 13.1 (q, C-8).

B.P. - 100°C/0.4 mm.(lit.[8] bp 85°/0.2mm).

*Note + The β-lactam 8 shows the parent peak at 128 (M + 1, 100%) in the EI Mass spectra which indicates that the β-lactam 8 has been protonated by an acid. This can possibly occur either in the column during purification or by atmosphere. The EI Mass spectra of a mixture of acetophenone and β-lactam 8 was taken and (M + 1) peaks were observed for acetophenone (121, 50%) and β-lactam 8 (128, 100%). When EI Mass spectra of acetophenone is run alone only M^+(120, 50%) peak is observed. The literature[8] reports several 4-substituted azetidinones showing (M + 1) peak in the EI Mass spectra and no M^+.

The copies of the spectra are attached in the appendix.

2. Preparation of 4-sec-butylazetidin-2-one(9)



9

To a stirred mixture of 1.2625g (5 mmoles) of CuI·MeSMe[17] in 20 ml of ether under argon at -50°C was added 7.5 ml (10 mmol) of sec-BuLi (1.35 M). The -50°C bath was replaced by a -20°C bath and the reaction solution was stirred at -20°C for 15 mins.. The -20°C bath was again replaced by a -50°C bath and 20 ml of dimethylsulfide was added. To this cuprate solution at -50°C was added a solution of 0.323g (2.5 mmoles) of azetidinone 6 in 5 ml of ether. The resulting brownish red solution was stirred at -50°C for 1 hr., poured into a mixture of 80 ml of satd. NH_4Cl and 20 ml of conc. NH_4OH, stirred for 10 mins. and extracted three times with ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (230 - 400 mesh); CH_2Cl_2 : acetone as eluent) to give 0.305g (96% yield) of 9.

Mass spectra + (CI, 70eV, 45°C) 128(M + 1, 100%); (EI, 70eV, 45°C), 128 (M + 1, 100), 111 (2%), 97 (1.4%), 84 (M-C_3H_7, 67%), 69 (M-C_4H_{10}, 81%), 56 (M-C_3H_5NO, 34%).

IR(neat)$\nu_{cm^{-1}}$ + 3250(s,broad, N-H stretch) 2925(s, C-H stretch), 1740(s, C=O stretch) 1460(m), 1420(w), 1375(m), 1190(m), 1045(w), 1025(w).

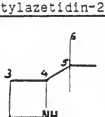
^{1}H NMR ($CDCl_3$)δ + 6.25 (broad peak, 1H, N-H), 3.35 (d,d,d, 1H, C-4H, J=2.2, 5, 10Hz), 2.97 (m, 1H, C-3H), 2.56 - 2.63 (m, 1H, C-3H), 1.4 - 1.52 (m, 1H, C-5H), 1.1 - 1.3 (m, 2H, CH_2), 0.8 - 1 (m, 6H, 2Me).

^{13}C NMR ($CDCl_3$)δ + 168.6 (s,C=O); 52.0, 52.4 (2d, C-4); 40.1, 40.8 (2t, C-3); 38.2, 38.3 (2d, C-5); 23.9, 24.7 (2t, C-6); 12.4, 13.2 (2q, CH_3); 9.3, 9.6 (2q, CH_3).

B.P.: 85°C/0.3mm.

Note: Except for C=O, 2 peaks are seen for every other carbon atoms of the 2 diastereoisomers.

3. Preparation of 4-t-butylazetidin-2-one(10)



10

To a stirred mixture of 1.2625g (5 mmoles) of CuI·MeSMe[17] in 20 ml of ether under argon at -50°C was added 5.6 ml (10 mmoles) of t-BuLi (1.8 M). The -50°C bath was replaced by a -20°C bath and the reaction solution was stirred at -20°C for 15 mins.. The -20°C bath was again replaced by a -50°C bath and 20 ml of dimethylsulfide was added. To this cuprate solution at -50°C was added a solution of 0.323g (2.5 mmoles) of azetidinone 9 in 5 ml of ether. The resulting brownish red solution was stirred at -50°C for 1 hr, poured into a mixture of 80 ml of satd. NH_4Cl and 20 ml of conc. NH_4OH, stirred for 10 mins. and extracted three times with ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (230 - 400 mesh; CH_2Cl_2: acetone as eluent) to give 0.285g (90% yield) of 10.

Mass Spectra + (CI, 70eV, 30°C) 128 (M + 1, 100%), (EI, 70eV, 25°C) 128 (M + 1, 19%), 99 (7.5%), 84 (M-C_3H_7, 100%), 69 (M-C_4H_{10}, 85%), 57 (M-C_3H_4NO, 83%).

IR (Nujol)ν_{cms}^{-1} + 3180 (s, broad, N-H), 2900 (s, C-H stretch), 1700 (s, broad, C=O stretch), 1460 (s), 1410 (w), 1350 (s), 1285 (w), 1210 (w), 1195 (s), 1010 (s), 980 (m), 960 (s), 935 (m).

^{1}H NMR ($CDCl_3$)δ + 6.25 (broad, 1H, N-H), 3.43 (d,d,d, 1H, C-4H, J=1.3, 2.6, 5Hz), 2.81 - 2.87 (m, 1H, C-3H, J=c.a. 1.2Hz), 2.68 (d,d,d, 1H, C-3H, J=1.3, 2.6, 15Hz), 0.92 (broad s, 9H, CMe_3).

^{13}C NMR ($CDCl_3$)δ + 168.8 (s, C=O), 56.7 (d, C-4), 38.2 (t, C-3), 31.7 (s, C-5), 24.5 (q, C-6).

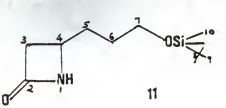
MP - 69°C.

4. (a) Preparation of 1-t-butyldimethylsilyloxy-3-lithiopropane

To 2.58g (10 mmoles) of 1-t-butyldimethylsilyloxy-3-bromopropane in 10 ml of ether under argon at room temperature was added 0.35g (0.05g. atoms) of finely cut lithium. After stirring at room temperature for 1 hr., the product (1-t-butyldimethylsilyloxy-3-lithiopropane) was taken for cuprate formation as shown in part (b).

Yield = 70%.

(b) Preparation of 4-t-butyldimethylsilyloxypropylazetidin-2-one(11)



11

To a stirred mixture of 0.884g (3.5 mmoles) of CuI·MeSMe[17] in 10 ml of ether under argon at -20°C was added a solution of 1-t-butyldimethylsilyloxy-3-lithiopropane (7.0 mmoles) in 10 ml of ether. The reaction solution was stirred at -20°C for 15 mins and then was added 20 ml of dimethylsulfide. This cuprate solution was cooled to -50°C and added a solution of 0.226g (1.75 mmoles) of azetidinone 6 in 6 ml of ether. The resulting reddish solution was stirred at -50°C for 30 mins., poured into a mixture of 80 ml of satd. NH_4Cl and 20 ml of conc. NH_4OH, stirred for 10 mins. and extracted three times with ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (230 - 400 mesh; CH_2Cl_2 : acetone as eluent) to give 0.420g (98% yield) of 11.

Mass Spectra + (CI, 70eV, 35°C) 244 (M + 1, 69%), (EI, 30eV, 35°C), 244 (M + 1, 4%), 186 (M-CMe_3, 74%), 156 (3%), 144 (100%), 101 (12%), 84 (40%), 75 (9%), 59 (15%).

IR (neat)ν_{cms}^{-1} + 3300 (m, broad, N-H stretch), 2900 (s, C-H stretch), 1730 (s, C=O stretch) 1460 (w), 1250 (m), 1100 (s), 840 (s), 780 (m).

^{1}H NMR ($CDCl_3$)δ + 6.04 (broad s, 1H, N-H), 3.64 (m, 3H, CH_2O and CHN), 3.05 (d,d,d, 1H, C-3H, J = 2.2, 5.0, 14.7Hz), 2.56 (d,d,d, 1H, C-3H, J = 1.3, 2.2, 14.7Hz), 1.7 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 0.9 (s, 9H, CMe_3), 0.04 (s, 6H, $SiMe_2$).

^{13}C NMR ($CDCl_3$)δ + 168.3 (s, C=0), 62.4 (t, C-7), 47.8 (d, C-4), 43.3 (t, C-3), 32.1 (t, C-5), 29.3 (t, C-6), 25.8 (q, C-9), 18.1 (s, C-8), -5.5 (q, C-10).

BP - 130°C/0.3mm.

5. (a) Preparation of 2-(2-bromoethyl)-1,3-dioxolane(19)[16]

To a stirred solution of 4g (0.05 moles) of HBr in 6.7g (0.108 moles) of ethylene glycol was added, at 5-10°C, 1.87g (0.033 moles) of acrolein. After stirring for 1 hr. at room temperature the mixture was extracted three times with hexane. The organic layer was washed with 5% $NaHCO_3$, dried (Na_2SO_4) and concentrated. Distillation of the residue afforded 3.6g (61% yield) of bromide 19.

B.P. - 65°C/5mm.

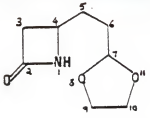
^{1}H NMR ($CDCl_3$)δ + 5.0 (t, 1H, CHO_2, J = 3.8Hz), 3.9 (m, 4H, $-O-CH_2-CH_2-O-$), 3.46 (t, 2H, CH_2Br, J = 6.4 Hz), 2.2 (m, 2H, CH_2).

(b) Preparation of 3,3-ethylenedioxypropylmagnesium bromide

The Grignard reagent was prepared by addition of 2.8g (15.5 mmoles) of bromide 19 in 10 ml of dry tetrahydrofuran (THF) under argon to 0.45g (0.0186 g atom) of magnesium over a period of 45 mins. at 30-35°C. Stirring was continued for 1 hr. at 30°C and the reagent was used up immediately for cuprate formation (Part c).

Yield = 70%.

(c) Preparation of 4-(3,3-ethylenedioxypropyl)-2-azetidinone(12)



12

To a stirred mixture of 1.369g (5.42 mmoles) of CuI·MeSMe[17] in 10 ml of ether under argon at -20°C was added the Grignard reagent (prepared in part b) (10.85 mmoles) in 10 ml of THF. The reaction solution was stirred at -20°C for 15 mins. and then was added 20 ml of dimethylsulfide. This cuprate solution was cooled to -50°C and added a solution of 0.35g (2.71 mmoles) of azetidinone 6 in 5 ml of ether. The reaction solution was stirred at -50°C for 15 mins. and then warmed to 0°C over a period of 45 mins. The resulting dark blue colored solution was poured into a mixture of 80 ml of satd. NH_4Cl and 20 ml of conc. NH_4OH, stirred for 10 mins. and extracted once with ether, followed by six extractions with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$) concentrated and flash chromatographed on silica gel (230 - 400 mesh; CH_2Cl_2 : acetone as eluent) to give 0.426g (92% yield) of 12.

Mass Spectra + (CI, 70eV, 110°C) 171 (M + 1, 70%), (EI, 70eV, 120°C), 170 (M^+, 8%), 141 ($M-C_2H_5$, 3%), 125 (10%), 98 (5%), 86 (5%), 72 (100%).

IR (neat) ν_{cms}^{-1} +- 3300 (s, broad, N-H), 2900 (s, C-H stretch), 1725 (s, C=O stretch), 1375 (s), 1275 (w), 1180 (w), 1125 (m), 1025 (m), 950 (m), 875 (m).

^{1}H NMR ($CDCl_3$)δ = 6.5 (broad s, 1H, N-H), 4.88 (t, 1H, CHO_2, J = 3.8Hz), 3.9 (m, 4H, CH_2O), 3.66 (m, 1H, C-4H), 3.03 - 3.09 (d,d,d, 1H, C-3H, J=1, 2.2, 14.8Hz), 2.57 (d,d,d, 1H, C-3H, J = 1.2, 2.2, 14.8Hz), 1.7 - 1.8 (m, 4H, CH_2 at C_5 and C_6)

^{13}C NMR ($CDCl_3$)δ = 168.0 (s, C=O), 103.5 (d, C-7), 64.6 (t, C_9 and C_{10}), 47.5 (d, C-4), 43.0 (t, C-3), 30.2(t) & 29.4(t) (C-5 & C-6).

6. (a) Preparation of vinyllithium

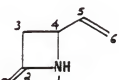
To a stirred solution of 2g (0.0187 moles) of vinylbromide in 20 ml of ether at -100°C (liquid nitrogen-pentane bath), is added 11.5 ml (0.0206 moles) of t-BuLi (1.8 M). After stirring at -100°C for 15 mins., the liquid nitrogen-pentane bath is replaced by a dry ice-acetone bath and the reaction contents are stirred at -78°C for 1 hr. The dry ice-acetone bath is next replaced by an ordinary ice bath and the reaction contents were stirred at 0°C for 1 hr.. After 1 hr. the reaction contents were warmed to room temperature. Vinyllithium was next standardized as shown in part (b).

(b) Standardization of vinyllithium

To 26 mg (0.122 moles) of diphenylacetic acid dissolved in 0.5 ml of THF at 0°C is added dropwise vinyllithium prepared as shown in part (a). End point of the titration is indicated by the solution turning yellow.

The prepared vinyllithium standardized in this manner was found to be 0.20M.

(c) Preparation of 4-vinylazetidin-2-one(13)



13

To a stirred mixture of 0.525g (2.08 mmoles) of CuI·MeSMe[17] in 5 ml of ether under argon at -30°C was added 25 ml of vinyllithium (0.20M). The reaction solution was stirred at -20°C for 15 mins. and then was added 30 ml of dimethylsulfide. This cuprate solution was cooled to -50°C and a solution of 0.107g (0.832 mmoles) of azetidinone 6 in 2 ml of ether is added. The resulting black solution was stirred at -50°C for 30 mins., poured into a mixture of 80 ml of satd. NH_4Cl and 20 ml of conc. NH_4OH, stirred for 10 mins. and extracted three times with ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (230 - 400 mesh; ethylacetate: Hexane as eluent) to give 60 mg (75% yield) of 13.

Mass Spectra + (CI, 70eV, 30°C), 97 (M^+, 44%), (EI, 70eV, 30°C) 97 (M^+, 44%), 80 (2%), 67 (13%), 53 (100%).

IR(Neat)ν_{cms}^{-1} + 3400 (m, N-H), 2950 (s, C-H stretch), 2690 (w), 2300 (s), 1740 (s, C=O stretch), 1410 (s), 1350 (m), 1250 (s), 1175 (m) 900 (s).

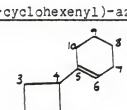
^{1}H NMR ($CDCl_3$)δ + 6.6 (broad s, 1H, N-H), 5.95 (m, 1H, C=C_5-H), 5.25 (d,d,2H, C=C_6 H, H, J=1, 10 Hz), 4.13 (m, 1H, C-4H), 3.2 (d,d,d, 1H, C-3H, J=2, 5.2, 14.8 Hz), 2.7 (d,d,d, 1H, c-3H, J = 1.3, 2.4, 14.8 Hz),

^{13}C NMR($CDCl_3$)δ + 167.4 (s, C=0), 137.5 (d, C-5), 117.1 (t, C-6), 49.5 (d, C-4), 45.2 (t, C-3).

7. (a) Preparation of 1-lithiocyclohexene

To 0.805g (5 mmoles) of 1-bromocyclohexene in 5 ml of ether under argon at room temperature was added 0.175g (0.025 g-atoms) of finely cut lithium. After stirring at room temperature for 1 hr., the product (1--lithiocyclohexene) was taken for cuprate formation as shown in part (b). Yield = 70%.

(b) Preparation of 4-(1-cyclohexenyl)-azetidin-2-one(14)



14

To a stirred mixture of 0.422g (1.75 mmoles) of CuI·MeSMe[17] in 5 ml of ether under argon at -20°C was added a solution of 1-lithiocyclohexene (3.5 mmoles) in 5 ml of ether. The reaction solution was stirred at -20°C for 15 mins. and then was added 10 ml of dimethylsulfide. This cuprate solution was cooled to -50°C and added a solution of 0.113g (0.875 mmoles) of azetidinone 6 in 3 ml of ether. The resulting dark green solution was stirred at -50°C for 30 mins., poured into a mixture of 80 ml of satd. NH_4Cl and 20 ml of conc. NH_4OH, stirred for 10 mins. and extracted three times

with ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (230-400 mesh), CH_2Cl_2; acetone as eluent) to give 0.125 g (95% yield) of 14.

Mass Spectra + (CI, 70 eV, 60°C) 152 (M + 1, 100%); (EI, 70eV, 50°C), 151 (M^+, 70%), 122 ($M-C_2H_5$, 21%), 108 ($M-C_3H_7$, 100%), 93 ($M-C_4H_{10}$, 76%), 79 (61%), 67 (48%), 53 (27%).

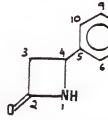
IR (Nujol)ν_{cms}^{-1} + 3175 (m, N-H stretch), 2880 (s, C-H stretch), 1700 (s, C=O stretch), 1450 (s), 1365 (s), 1260 (m), 1175 (m), 910 (w).

^{1}H NMR ($CDCl_3$)δ + 6.8 (broad s, 1H, N-H), 5.64 (broad s, C=C-H), 3.95 (m, 1H, C-4H), 2.97 - 3.04 (d,d,d, 1H, C-3H, J=1.75, 3.4, 15.1 Hz), 2.62 (d,d,d, 1H, C-3H, J=1.3, 1.3, 14Hz), 1.82 - 1.96 (m, 4H, CH_2 at C_7 and C_{10}), 1.44 - 1.65 (m, 4H, CH_2 at C_8 and C_9).

^{13}C NMR ($CDCl_3$)δ + 168.4 (s, C=O), 135.8 (s, C-5), 123.2 (d, C-6), 51.8 (d, C-4), 43.2 (t, C-3), 24.7(t), 23.3(t) (C-7 & C-10), 22.2 (t, 2C, C_8 and C_9).

M.P. - 60°C.

8. Preparation of 4-phenylazetidin-2-one(15)



15

To a stirred mixture of 1.2625g (5 mmoles) of CuI·MeSMe[17] in 20 ml of ether under argon at -20°C was added 5 ml (10 mmoles) of PhLi (2M). The reaction solution was stirred at -20°C for 15 mins. and then was added 20 ml of dimethylsulfide. To this cuprate solution was added a solution of 0.32g (2.5 mmol) of azetidinone 6 in 10 ml of ether. The resulting greenish solution was stirred at -20°C for 1 hr., poured into a mixture of 80 ml of satd. NH_4Cl and 20 ml of conc. NH_4OH, stirred for 10 mins. and extracted three times with ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (230 - 400 mesh; CH_2Cl_2: acetone as eluent) to give 0.3 g (82% yield) of 15.

Mass Spectra + (CI, 70 eV, 150°C), 148 (M + 1, 100%); (EI, 70eV, 130°C), 147 (M^+, 15%), 118 (M-CHO, 12%), 104 (M-$\overset{\overset{O}{\|}}{C}$-NH, 100%), 91 (3%), 77 (14%), 63 (3%).

IR (Nujol)ν_{cms}^{-1} + 3150 (m, broad, N-H stretch), 2900 (s, C-H stretch), 1675 (s, C=O stretch), 1450 (m), 1360 (m), 1175 (m), 1000 (w), 975 (w), 960 (w).

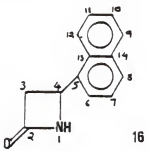
^{1}H NMR ($CDCl_3$)δ + 7.3 (m, 5H, Arom. H), 6.3 (broad s, 1H, N-H), 4.73 (d,d, 1H, C-4H, J = 2.52, 5.3 Hz), 3.44 (d,d,d, 1H, C-3H, J = 2.5, 5.3 14.9 Hz).

^{13}C NMR ($CDCl_3$)δ + 168.4 (s, C=O), 140.2 (s, C-5), 128.7 (d, 2C, C_6 and C_{10}), 128 (d, C-8), 125.5 (d, 2C, C_7 and C_9), 50.2 (d, C-4), 47.7 (t, C-3). M.P. - 106°C.

9. (a) Preparation of 1-lithionaphthalene

To 3.44 g (16.7 mmoles) of 1-bromonaphthalene in 10 ml of ether under argon at room temperature was added 0.588g (0.084 gm atoms) of finely cut lithium. After stirring at room temperature for 1 hr., the product (1-lithionaphthalene) was taken for cuprate formation as shown in part (b). Yield = 60%.

(b) Preparation of 4-[1-naphthyl]azetidin-2-one(16)



16

To a stirred mixture of 1.2625g (5 mmoles) of CuI·MeSMe[17] in 20 ml of ether under argon at -20°C was added a solution of 1-lithionaphthalene (10 mmoles) in 10 ml of ether. The reaction solution was stirred at -20°C for 15 mins., cooled to -50°C and 20 ml of MeSMe was added. To this cuprate solution at -50°C, was added a solution of 0.32 g (2.5 mmoles) of azetidinone 6 in 5 ml of ether. The resulting dark green colored solution was stirred at -50°C for 1 hr., poured into a mixture of 80 ml of satd. NH_4Cl and 20 ml of conc NH_4OH, stirred for 10 mins. and extracted three times with ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (230 - 400 mesh; CH_2Cl_2: acetone as eluent) to give 0.39 g (80% yield) of 16.

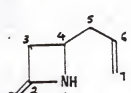
Mass Spectra + (CI, 70eV, 30°C) 197 (M + 1, 23%); (EI, 20eV, 35°C), 196 (M^+, 8%), 178 (40%), 169 (23%), 155 (36%), 149 (30%), 140 (28%), 127 (36%), 117 (53%), 111 (47%), 100 (6%), 83 (100%), 76 (13%), 69 (97%), 56 (46%).

IR (Nujol)ν_{cms}^{-1} + 3200 (w, N-H stretch), 2850 (s, C-H stretch), 1725 (s, C=O stretch), 1450 (s), 1360 (m), 1320 (w), 775 (s).

^{1}H NMR ($CDCl_3$)δ + 7.81 - 7.93 (m, 3H, Arom. H), 7.47 - 7.59 (m, 4H, Arom. H), 6.4 (broad s, 1H, N-H), 5.42 (d,d, 1H, C-4H, J = 2.7, 5.3 Hz). 3.7 (d,d,d, 1H, C-3H, J=2.7, 5.4, 14.6 Hz), 2.9 (d,d, 1H, C-3 H, J=2.7, 14.7 Hz).

^{13}C NMR ($CDCl_3$)δ + 169 (s, C=O), 131, 135, 137 (s, C_5, C_{13}, C_{14}), 121-130 (d, 7C, C_6 - C_{12}), 49 (d, C-4), 47 (t, C-3).

10. Preparation of 4-allylazetidin-2-one(17)



17

To a stirred mixture of 0.422g (1.75 mmoles) of CuI·MeSMe[17] in 5 ml of ether under argon at -30°C was added 9.2 ml (3.5 mmoles) of allyllithium (0.38 M). After stirring at -30°C for 10 mins., the -30°C bath was replaced by a -50°C bath and 10 ml of dimethylsulfide was added. To this cuprate solution was added 0.113g (0.87 mmoles) of azetidinone 6 in 5 ml of ether. The resulting dark brown solution was warmed to -30°C over a period of 1 hr., poured into a mixture of 80 ml of satd. NH_4Cl and 20 ml of conc. NH_4OH, stirred for 10 mins. and extracted three times with ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (230 - 400 mesh; ethylacetate: Hexane as eluent) to give 69 mg (71% yield) of 17.

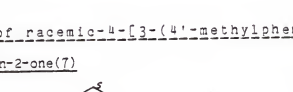
Mass Spectra + (CI, 70eV, 30°C) 111 (M^+, 100%); (EI, 70eV, 30°C), 111 (M^+, 67%), 103 (14%), 95 (12%), 82 ($M-C_2H_5$, 11%), 77 (1.5%), 69 (100%), 66 (57%), 52 (36%).

IR (Neat) $\nu_{cms^{-1}}$ 3250 (s, N-H stretch), 2900 (m, C-H stretch), 1725 (s, C=O stretch), 1350 (m), 1180 (m), 1060 (m), 910 (s).

^{1}H NMR ($CDCl_3$)δ 6.7 (broad s, 1H, N-H), 5.8 (m, 1H, C=C_6-H), 5.12 (m, 2H, C_6=C_7<H, H>), 3.68 (m, 1H, C-4H), 3.03 (d,d,d, 1H, C-3H, J=1.9, 4.9, 14.8 Hz), 2.6 (d,d,d, 1H, C-3H, J = 1.35, 2.2, 14.8 Hz), 2.48 (m, 2H, CH_2 at C-5).

^{13}C NMR ($CDCl_3$)δ - 168 (s, C=O), 133 (d, C-6), 117.8 (t, C-7), 46.9 (d, C-4), 42.7 (t, C-3), 39.3 (t, C-5).

11. Preparation of racemic-4-[3-(4'-methylphenylsulfinyl)-2-propenyl]azetidin-2-one(7)



To 0.495g (0.00275 moles) of racemic allylsulfoxide in 7 ml of THF under argon at -78°C was added 0.00275 moles of lithium diisopropylamide (LDA) [0.00275 moles of diisopropylamine, 0.00275 moles of nBuLi (1.6 M) in 7 ml of THF] at -78°C. After stirring at -78°C for 1 hr., 0.16g (0.00138 moles) of azetidinone 6 in 5 ml of THF was added. The resulting solution was stirred at -78°C for 1 hr., diluted with satd. NH_4Cl, extracted thrice with methylene chloride, dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (230 - 400 mesh; CH_2Cl_2 : acetone as eluent) to give 42 mg (14% yield) of 7.

Mass Spectra + (CI, 70 eV, 170°C), 250 (M + 1, 100%); (EI, 70eV, 160°C) 249 (M^+, 2%), 246 (10%), 201 (15%), 158 ($M-C_6H_4CH_3$, 39%), 139 (37%), 130 (20%), 123 (100%), 110 (11%), 91 (89%), 76 (37%), 65 (79%).

^{1}H NMR ($CDCl_3$)δ + 7.5 (m, 2H, Arom. H), 7.35 (m, 2H, Arom. H), 6.6 (broad s, 1H, N-H), 6.5 (m, 1H, $C=C_6-H$), 6.3 (d, 1H, $C=C_7-H$), 3.7 (m, 1H, C-4H), 3.06 (m, 1H, C-3H), 2.63 (m, 1H, C-3H), 2.4 (broad s, 3H, $p-CH_3$), 2.1 - 2.7 (m, 2H, CH_2 at C-5).

^{13}C NMR ($CDCl_3$)δ + 167.1 (s, C=0), 141.8 (s, C-8), 140.3 (s, C-11), 138.1 (d, C-7), 133.3 (d, C-6), 130.1 (d, 2C, C-9 & C-13), 124.6 (d, 2C, C-10 & C-12), 46.3 (d, C-4), 43.2 (t, C-3), 37.6 (t, C-5) 21.3 (q, C-14).

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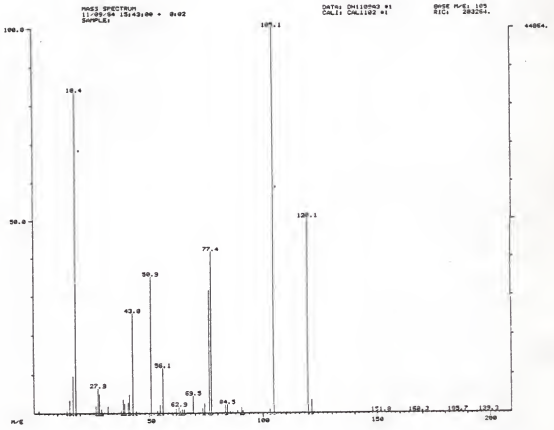
APPENDIX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SAMPLE1
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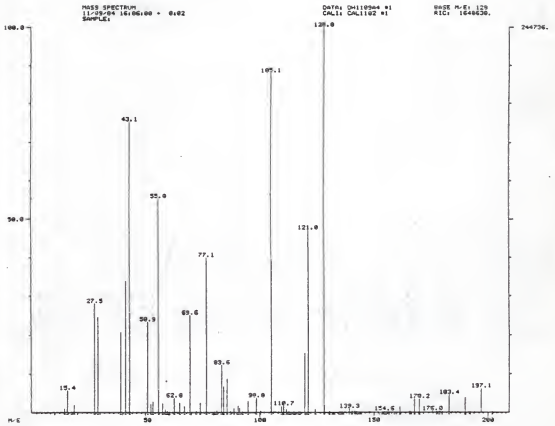
CALI: CAL1102 #1
BASE M/E 105
RIC: 283264.
44864.
100.0
50.0
M/E
18.4
27.9
43.0
50.9
56.1
62.9
69.5
77.4
84.5
105.1
120.1
151.9
158.2
193.7
229.3
50
100
150
200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11/30/94 16:06:00 + 0:02
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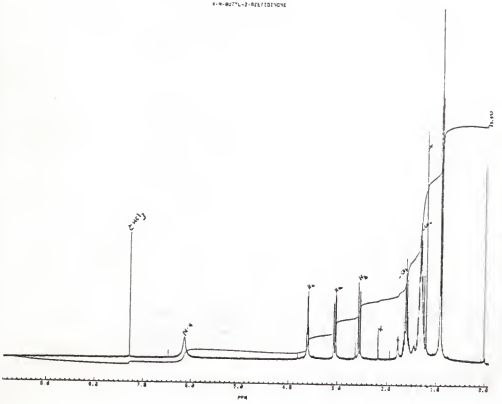
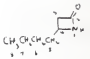
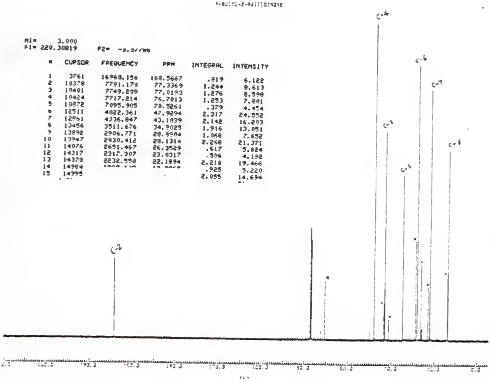
CAL1: CAL1102 #1
BASE M-E: 129
RIC: 1648630.
100.0
50.0
M-E
244736.
129.0
107.1
43.1
55.0
121.0
77.1
27.5
50.9
69.6
83.6
15.4
62.0
90.0
118.7
139.3
154.6
175.0
179.2
183.4
197.1
50
100
150
200

AGV-II-004







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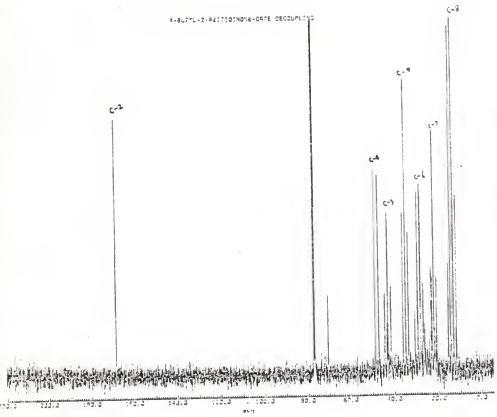
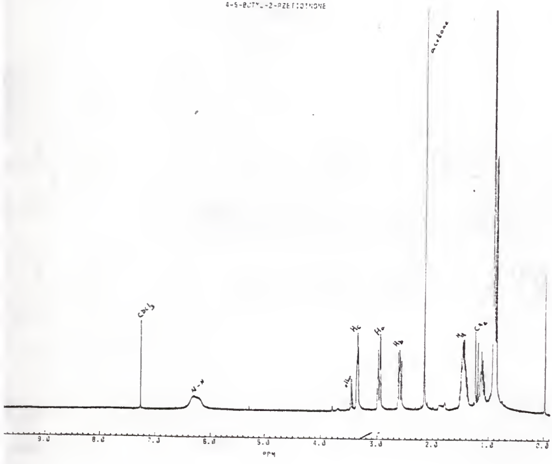
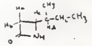
2	10379	7781.170	77.3369	1.244	8.613
3	10401	7749.209	77.0193	1.276	8.599
4	10424	7717.214	76.7013	1.253	7.801
5	10872	7095.905	70.5261	.379	4.454
6	12511	4822.361	47.9294	2.317	24.552
7	12861	4336.847	43.1039	2.142	16.203
8	13456	3511.676	34.9025	1.916	13.051
9	13892	2906.771	28.9904	1.068	7.652
10	13947	2930.412	28.1314	2.268	21.371
11	14076	2651.467	26.3529	.617	5.824
12	14317	2317.307	23.0317	.506	4.192
13	14378	2232.558	22.1894	2.218	19.466
14	14984	[illegible]	[illegible]	.925	5.220
15	14995	[illegible]	[illegible]	2.055	14.694


4-BUTYL-2-AZETIDINONE-DEPT DECOUPLED
C-2
C-3
C-4
C-5
C-6
C-7
C-8
C-9
PPM


O
NH
CH3CH2CH2CH2
8 7 6 5
1
2
3
4

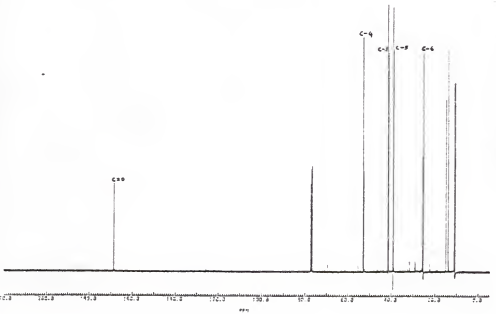
4-S-BUTYL-2-AZETIDINONE

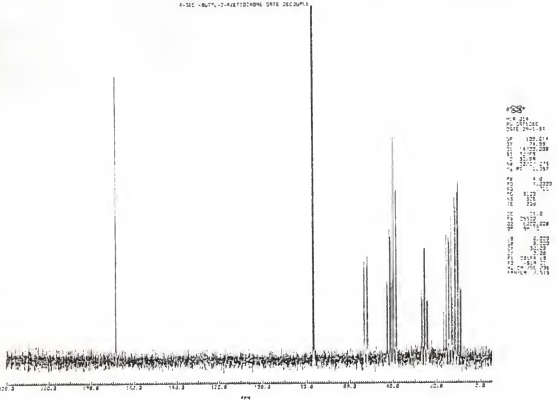




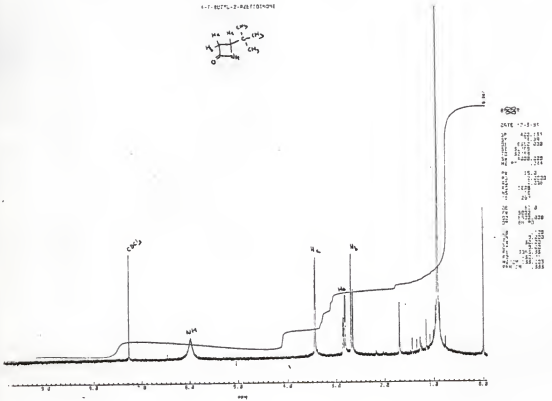
DATE 12-3-94

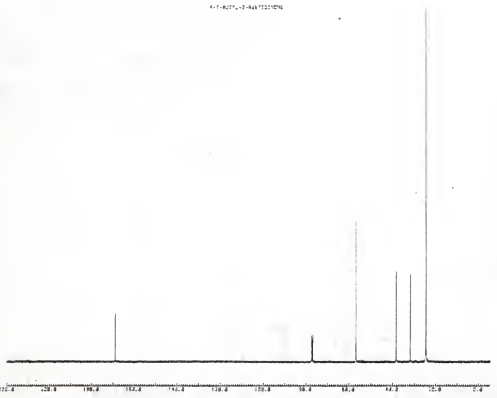
^{13}C-NMR





AGV-II-006





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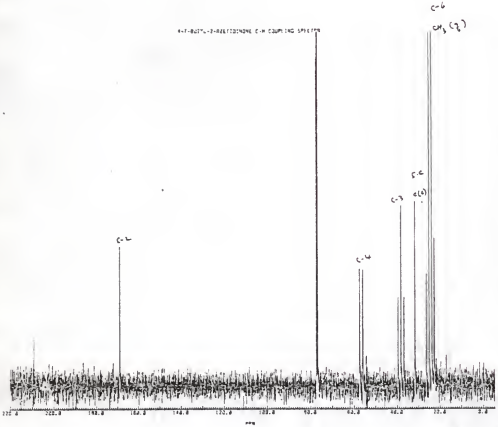

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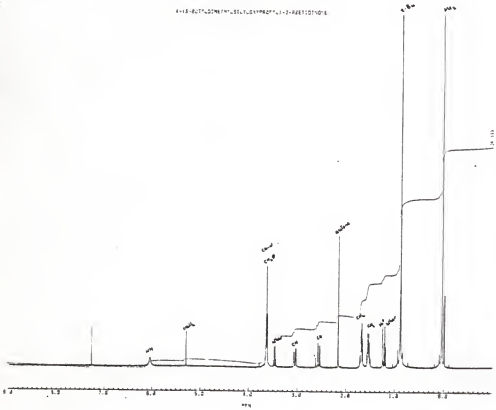

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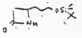
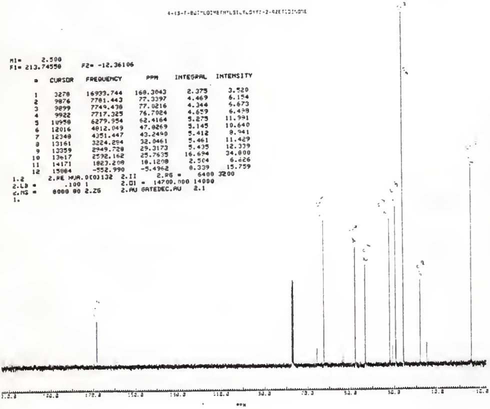


4-(3-T-BUTYLDIMETHYLSILYLOXY)-2-AZETIDINONE



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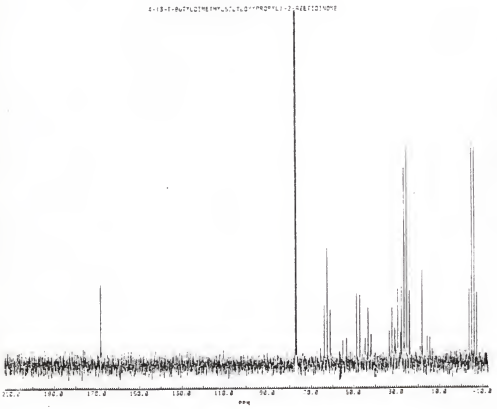
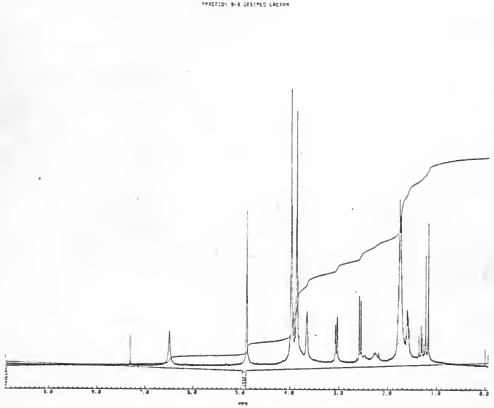
2	9876	7781.443	77.3397	4.469	6.154
3	9899	7749.438	77.0216	4.344	6.673
4	9922	7717.325	76.7024	4.659	6.498
5	10958	6279.954	62.4164	5.275	11.991
6	12016	4812.049	47.8269	5.145	10.640
7	12348	4351.447	43.2490	5.412	8.941
8	13161	3224.294	32.0461	5.461	11.429
9	13359	2949.728	29.3173	5.435	12.339
10	13617	2592.162	25.7635	16.694	34.800
11	14171	1823.208	18.1208	2.504	6.626
12	15864	-552.990	-5.4962	8.339	15.759

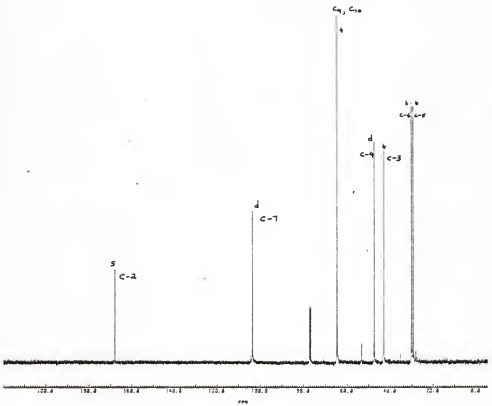
1.2 2.RE MJA.0(0)132 2.II 2.RG = 6400 3200
2.LB = .100 1 2.D1 = 14700.000 14000
2.NS = 8000 80 2.ZG 2.AU GATEDEC.AU 2.1
1.

Contained small amounts acetone, CH_2Cl_2 and ? (by ^1H NMR)

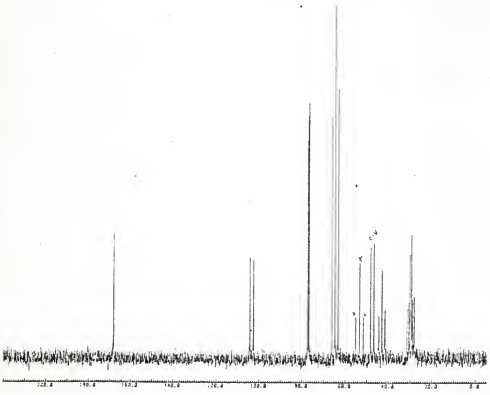

ppm


FRACTION 9-9 DESIRED LACTAM
DATE 9-7 84
PPM

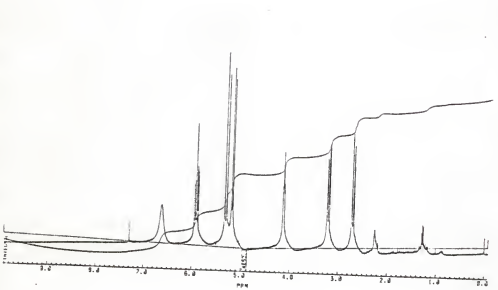
^{13}C — NMR

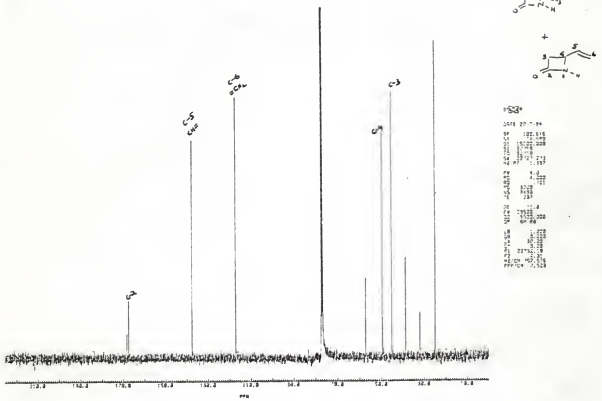


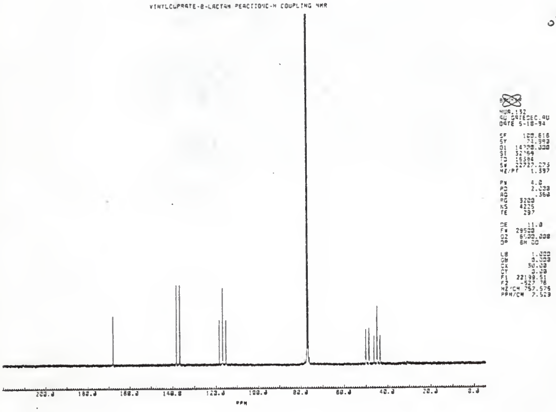
C-H coupling NMR



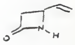
VINYLCUPRATE 8- LACTON REACTION



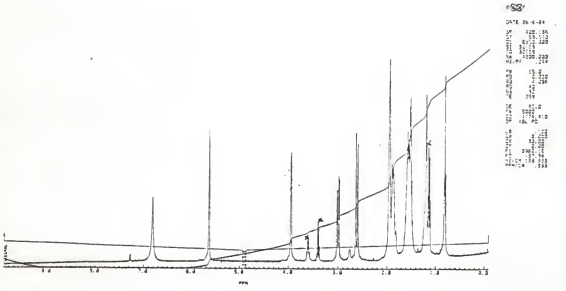




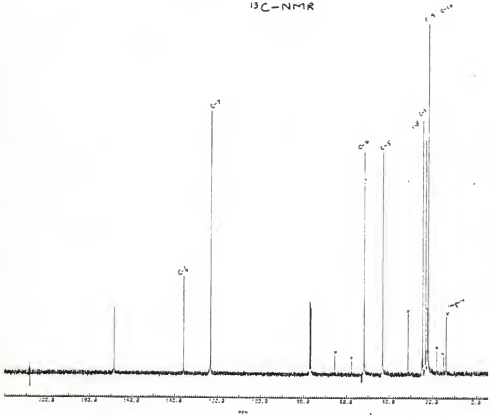
VINYLCUPRATE-B-LACTAM REACTIONC-H COUPLING NMR
200.0 180.0 160.0 140.0 120.0 100.0 80.0 60.0 40.0 20.0 0.0
PPM
DATE 5-18-94
SF 100.616
NS 4225
TE 297
LB 1.000
PPM/CM 7.529

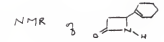


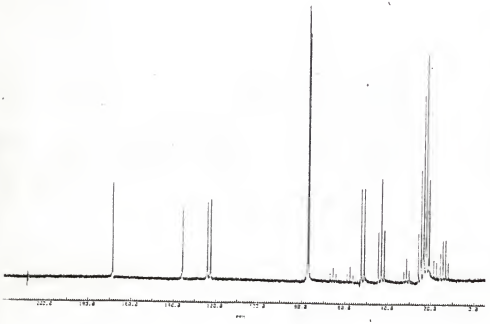
O
N
H

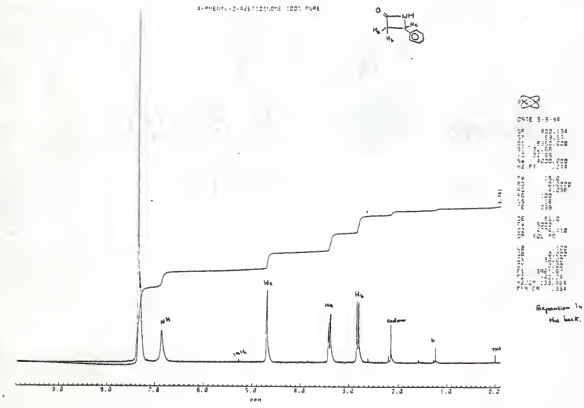


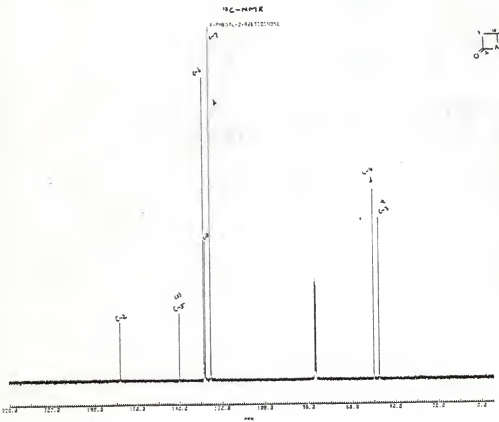
^{13}C-NMR

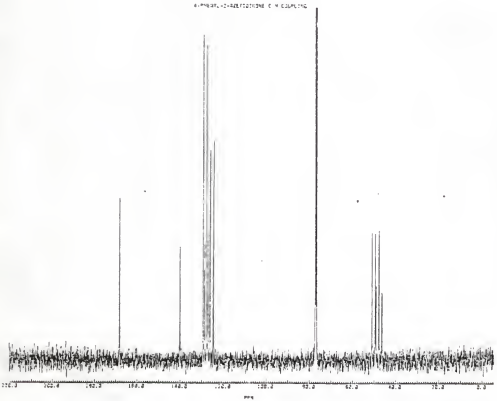


C-H coupling NMR of  AGV-II-041c

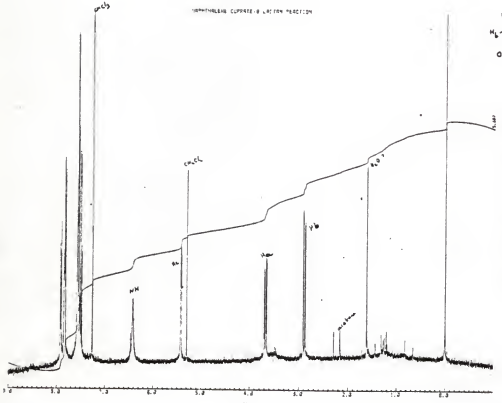



4-PHENYL-2-AZETIDINONE 100% PURE
DATE 5-3-96
Expansion in the back.
NH
Ha
Hb
Hc
acetone
ppm


13C-NMR
PPM

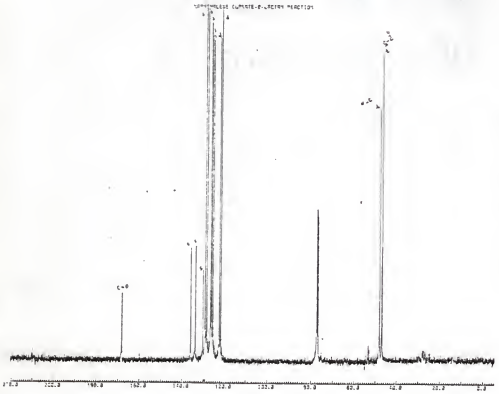


AGV-II-010'

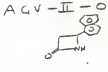


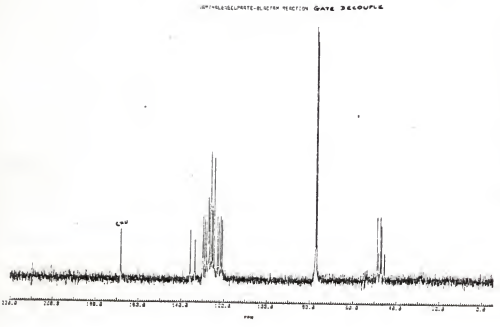
AGV – II – 013

^{13}C-NMR

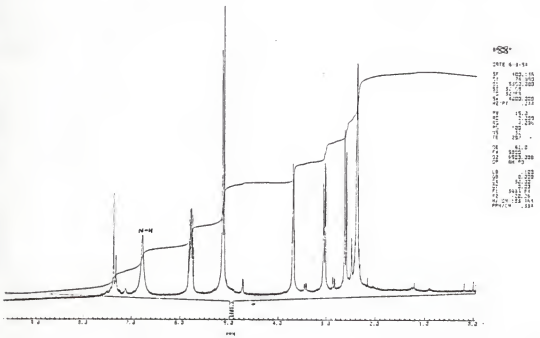


AGV-II-012²

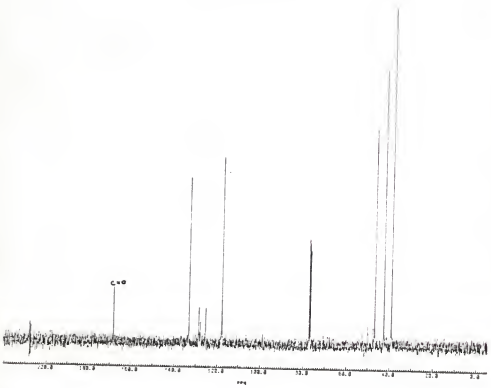


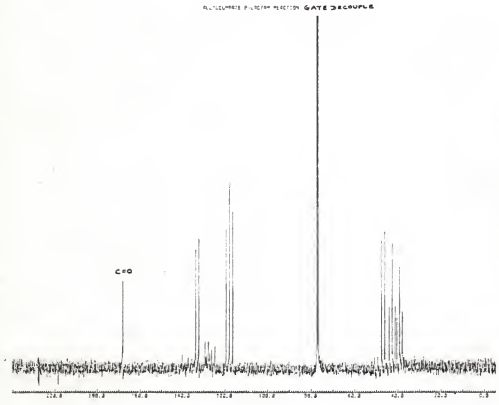


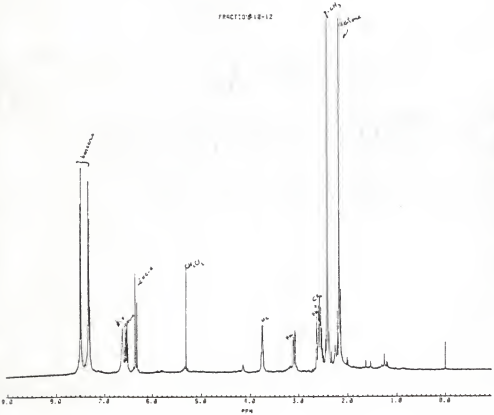
ALLYL CUPRATE - β-LACTAM REACTION



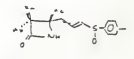
^{13}C-NMR

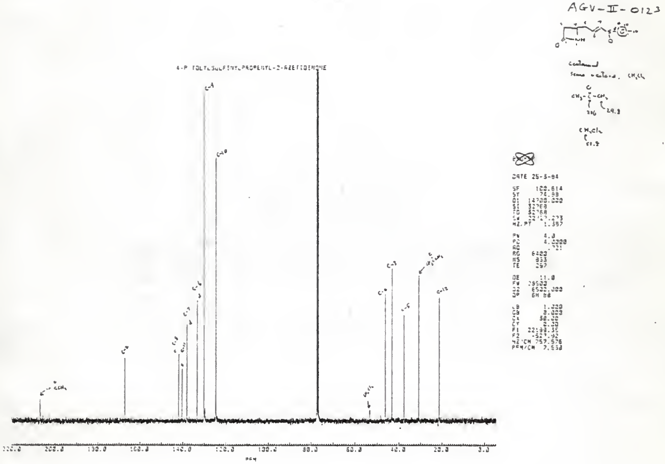



GATE DECOUPLE
C=O



AGV-II-012a




AGV-II-0123
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DATE 25-3-84
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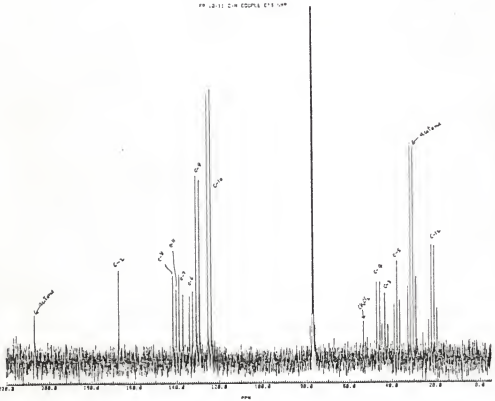

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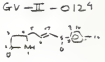

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SYNTHESIS OF 4-SUBSTITUTED 2-AZETIDINONES

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ABSTRACT

4-Substituted 2-azetidinones can be obtained in excellent yields from the reactions of various cuprates with 4-acetoxy-2-azetidinone. When 4-acetoxy-2-azetidinone was treated with one equivalent of the cuprates in ether: dimethylsulfide (1:1) at -50°C to -30°C, only 20-30% of the corresponding 4-substituted 2-azetidinones were obtained. However when two equivalents of the cuprates were used, the yields were excellent (71-98%). By this method we have been able to introduce alkyl, aryl, allyl and alkenyl groups at the 4-position of 2-azetidinones in excellent yields.