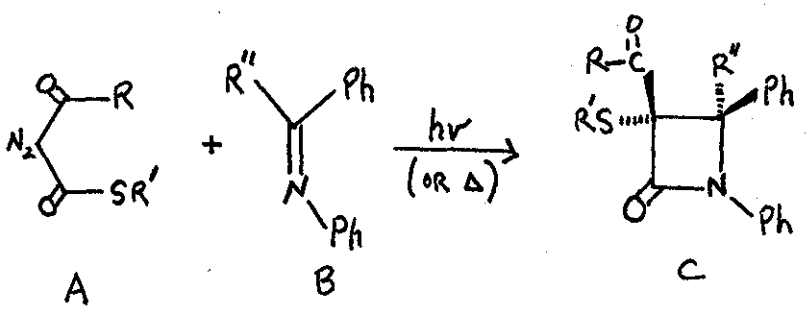
A NEW SYNTHESIS OF β-LACTAMS
REARRANGEMENTS OF α-DIAZO THIOESTERS†

Vlasios Georgian*, Stephen K. Boyer[1], Brooks Edwards
Department of Chemistry, Tufts University
Medford, Massachusetts 02155

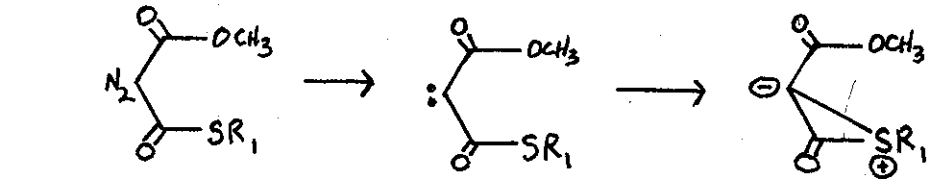
A new synthesis of alkylthio-substituted β-lactams by the rearrangement of α-diazo thioesters has been developed.

New methods of constructing β-lactam ring systems are of particular importance in the synthesis of analogs of penicillin and cephalosporin[2]. In this report we describe examples of a novel procedure for the preparation of β-lactams which may offer advantages over currently available methods. The key feature of this synthetic method involves the thermally or photochemically initiated rearrangement of methyl α-diazo-α-(alkylthio)carbonyl-acetates, compounds of type A. These compounds upon rearrangement in the presence of a suitable imine acceptor B lead to the generation of β-lactams C.



A B C

Our preferred mechanistic interpretation of this rearrangement, shown in Scheme 1, involves the direct participation of sulfur, via the formation of a sulfonium ylide (3). This then rearranges to an alkylthio-substituted ketene (4), capable of undergoing a cycloaddition to form the observed β-lactam (6). Similar participation of sulfur has been proposed in rearrangements of related systems[3]. This probably accounts for the overall selectivity of the migrating group.



1a (R_1=CH_3)
b (R_1=CH_2Ph)

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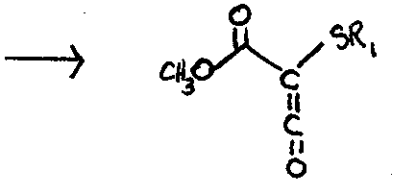
3



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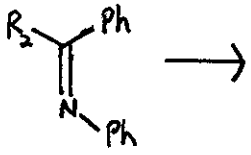
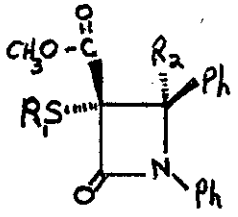


5a (R_2=H)
b (R_2=SCH_3)



6a (R_1=CH_3, R_2=H)
b (R_1=CH_2Ph, R_2=H)
c (R_1=CH_3, R_2=SCH_3)

Reagents of type A are readily obtained as exemplified by the preparation of 1a[4]. Methyl malonyl chloride[5] was caused to react with methyl mercaptan in anhydrous ether at 0°C upon addition of one equivalent of pyridine to yield methyl (methylthio)-carbonylacetate in 80% yield (b.p. 55-58°/0.075 mm; ir (neat) (cm^{-1}), 2950 (C-H), 1740 (C=O), 1682 (C=O); nmr ($CDCl_3$, δ): 3.82 (s, 3H, OCH_3), 3.60 (s, 2H, CH_2), 2.33 (s, 3H, SCH_3)). Diazo-functionalization of this compound with tosyl azide, according to known procedure[6], gave 1a in 77% yield (m.p. 53° (from cyclohexane); ir ($CHCl_3$) 2120 (diazo), 1710 (broad, C=O); nmr ($CDCl_3$, δ); 3.70 (s, 3H, OCH_3), 2.35 (s, 3H, SCH_3))[7].

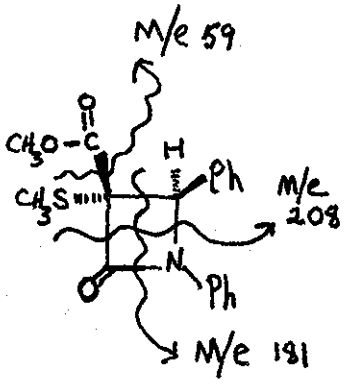
Irradiation[8] of 1a (174 mg, 1 mmol) in the presence of N-benzylidenaniline[9] (5a) (181 mg, 1 mmol) in $CDCl_3$ (3 mL) afforded after removal of solvent and trituration with cyclohexane/ether 167 mg (isolated) of trans methyl 1,4-diphenyl-3-methylthio-2-azetidinone-3-carboxylate (6a) m.p. 125°C (from cyclohexane/ether) ir ($CDCl_3$) (cm^{-1}) 1745 (β-lactam, C=O), 1710 (C=O), 1380, 1255; nmr ($CDCl_3$, δ): 7.30-7.10 (m, 10H, Ph) 5.01 (s, 1H, β-lactam), 3.23 (s, 3H, OCH_3), 2.20 (s, 3H, SCH_3): $C_{18}H_{17}NO_3S$, M^+= 327 m/e. However, the reaction appeared to be quantitative by nmr, as no other products other than 6a and a trace amount of starting material were observed in the crude reaction mixture. No effort was made to optimize the isolation procedure.

The progress of the reaction (6a) was monitored by nmr. It was possible to observe the shift of the methoxy peak from 3.7 ppm to 3.2 ppm; also observed was the disappearance of the N-benzylideneaniline imine proton at 8.2 ppm and its reappearance

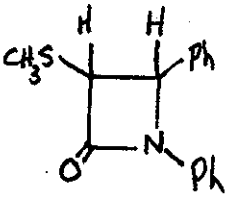
as a β-lactam proton at 5.06 ppm. The relative intensities of tnese changes in the nmr corresponded to the disappearance of the diazo (2150 cm^{-1}) and imine double bond bands (1650 cm^{-1}) in the ir.

A similar yield of 6a was obtained thermally by refluxing equimolar amounts of 1a and 5a in tetrachloroethylene.

The β-lactam structure 6a was assigned from the H^1-nmr, and ir spectroscopic data. In addition, the C-13 nmr of 6a showed two carbonyl carbon atoms at 167 ppm and 162 ppm, and the mass spectrum shows a pattern consistent with the β-lactam structure 6a.



6a



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The overall stereoselectivity of the reaction, i.e., sulfur cis to hydrogen, was determined by nuclear Overhauser experiments on compound 6a[9]. The β-lactam proton showed a 26% enhancement on irradiation of the methylthio group. This nuclear Overhauser datum helps further to confirm assignment of structure 6a.

By this general procedure the following substituted β-lactams were also prepared 6b: m.p. 143-145°C (from cyclohexane/acetone); ir (Nujol mull) 1750 cm^{-1} (β-lactam, C=O), 1730 C=O; 1380, 1260.

nmr ($CHCl_{3,\delta}$) 7.4-6.9 (m, 15H, Ph), 4.86 (s, 1H, β-lactam), 4.12 (s, 2H, CH_2); 3.12 (s, 3H, OCH_3). $C_{29}H_{21}NO_3S$, M^+=403 m/e and 6c; m.p. 142-144°C (from cyclohexane/acetone); ir (Nujol) 1760 (β-lactam, C=O), 1740 cm^{-1} (C=O); 1375, 1250; nmr ($CDCl_{3\delta}$) 7.8-6.9 (m, 10H, Ph), 3.93 (s, 3H, OCH_3), 2.12 (s, 3H, SCH_3), 2.00 (s, 3H, SCH_3). $C_{19}H_{19}NO_3SO_2$, M^+= 373 m/e.

The advantages of this particular method of the synthesis of β-lactams are several; unlike other ketene precursors such as the commonly employed azidoacetyl chloride, the compounds of type A are stable in the presence of a variety of imine acceptors and thus do not undergo side reactions prior to ketene formation[10]; the necessity of using external base to generate a ketene, which in many cases alters the desired course of reaction, is avoided; the reaction appears to be stereoselective and offers interesting functionalization of the β-lactam ring which allows for a variety of synthetic goals.

For example, it has been shown that methylthio-substituted β-lactams can be converted, with retention of configuration, to the unsubstituted derivatives[11,12](via Raney nickel) or the corresponding methoxy-substituted compounds (via $Hg(OA_c)_2$)[12]. In addition, we have observed the decarbomethoxylation of 6a (LiI, pyridine, reflux 6 hours) which results in the obtention of 10 in quantitative yield as a mixture of stereoisomers (~50:50 via nmr). This demonstrates the feasibility of our synthetic route to alkylthio-substituted β-lactams. Applications of this approach to the construction of novel penicillin and cephalosporin models are currently under active investigation in these laboratories.

Footnotes

† Dedicated to Professor R. B. Woodward for his sixtieth birthday.

1) Present address: CIBA-GEIGY Corporation, 180 Mill Street, Cranston, Rhode Island 02905.

2) E. H. Flynn, Ed., "Cephalosporins and Penicillins: Chemistry and Biology," Academic Press, New York, New York 1972.

3) S. S. Hixson and S. H. Hixson, J. Org. Chem., 37, 1279 (1972).

4) Other reagents of type A which were prepared include (R=OCH_3; R' = allyl, phenyl, t-butyl) and (R = CH_3, R' = methyl).

5) H. Staudinger and H. Becker, Chem. Ber. 50, 1023 (1911).

6) S. Julia, et.al., Bull. Soc. Chim. Fr., 4913 (1968).

7) All crystalline compounds had satisfactory elemental analyses.

8) Hanovia 450 watt mercury arc, with pyrex filter.

9) We wish to thank Dr. Homer Pierce/Harvard University for performing the Nuclear Overhauser experiments.

10) For example, see B. T. Golding and D. R. Hall, J. Chem. Soc. (Perkin I), 1202 (1975).

11) A. K. Bose, M. S. Manhas, J. S. Chib, H.P.S. Chawla and B. Dayal, J. Org. Chem. 39, 2877 (1974), and references therein. Brooks Edwards, Tufts University, unpublished results.

12) W. A. Slusarchyk, W. Koster, et.al., J. Org. Chem. 38, 943 (1973).

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