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CARBON NUCLEOPHILIC DISPLACEMENTS ON KAMIYA'S AZETIDINONE DISULFIDE: SYNTHESIS OF C-2 MODIFIED PENICILLINS

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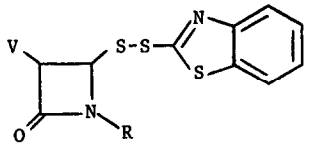
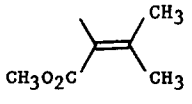
Summary: Novel carbon nucleophilic displacement reactions on Kamiya's azetidinone disulfide 2 and the synthesis of the C-2 modified penams 25, 26 and 27 from the intermediates 8, 9, and 11 are described.

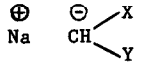
Kamiya's azetidinone disulfide 1[1], readily available from penicillin, has been extensively utilized for the synthesis of C-2β-halomethyl penams[2], cephems[2], and penems[3]. In this paper, we report the carbon nucleophilic displacements on the azetidinone 2 (obtained in 70% crystalline yield from 1 by ozonolysis followed by treatment with methanol[3]) and application of this reaction for the preparation of C-2 modified penams. The azetidinone 2 reacted at 0° in tetrahydrofuran with the stable carbanions 3-7 to give the 2-azetidinones 8-12 in yields of 72-90%. Similarly, reaction of 2 with the enamine 13 gave 14 in 67% yield after acidic work up. Stabilized ylides 15 and 16 also cleanly displaced the disulfide 2 to give the ylides 17 and 18 in yields of 97% and 91%, respectively.

A typical experimental procedure is as follows: To NaH (57%, 90 mg) in 15mL of dry THF at 0° was added a solution of 264 mg (2.0 mmol) of dimethyl malonate in 3 mL of THF. After hydrogen evolution had ceased, a solution of 417 mg (1.0 mmol) of 2 in 5 mL of THF was added dropwise and stirred for 45 min at 0° under N_2. The reaction was diluted with EtOAc and then sequentially washed with 20% H_3PO_4 and brine. Silicagel chromatography of the concentrate of the dried organic phase gave 310 mg (81%) of 8[4] as a colorless oil. NMR ($CDCl_3$) δ 3.82 (s, 6H), 4.25 (s, 1H) , 4.50 (s, 2H), 5.28 (d, J=7.0Hz, 1H), 5.53 (q, J=7.0, 9.5 Hz, 1H), and 6.8-7.4 (m, 6H).

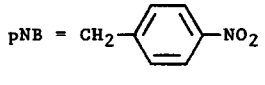


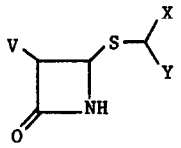
1, R = 

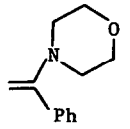
2, R = H



3, X = Y = CO_2CH_3
4, X = CO_2CH_3, Y = CO_2pNB
5, X = Y = CN
6, X = Y = SO_2CH_3
7, X = Y = $COCH_3$

V = $PhOCH_2CONH$ pNB = 





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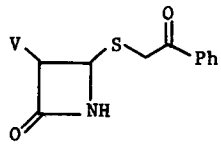
8, X = Y = CO_2CH_3 (81%)
9, X = CO_2CH_3, Y = CO_2pNB (78%)
10, X = Y = CN
11, X = Y = SO_2CH_3 (72%)
12, X = Y = $COCH_3$ (82%)



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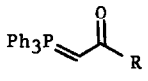
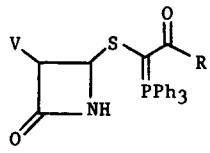


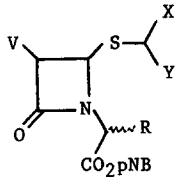
15, R = OCH_3
16, R = CH_3

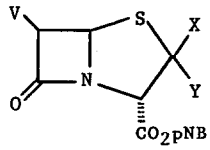


17, R = OCH_3 (97%)
18, R = CH_3 (91%)

In all cases, coupling constants of 5.5-7.0 Hz in the ^{1}H-nmr indicated that cis stereochemistry was maintained for the C-3 and C-4 azetidinone substituents.

We next turned our attention to the utilization of the carbon displaced intermediates for the synthesis of penicillin derivatives. Azetidinones 8, 9, and 11 were smoothly condensed with p-nitrobenzyl glyoxylate[5] to give the mixed epimers of the α-hydroxyesters 19, 21 and 23. Reaction with thionyl chloride then gave the epimeric chlorides 20, 22, and 24, which upon exposure to triethylamine underwent ring cyclization to furnish the penams 25[6], 26[6], and 27[7] in about 40% overall yield in each case. The new penams are obtained as mixtures of epimers at C-3. Catalytic hydrogenation (Pd/C, THF) of 25 and 26 gave single isomers 28[6] and 29[6] in yields of 28% and 32%, respectively. The stereochemistry of 29 was assigned by a ^{1}H-nmr decoupling study. Double irradiation experiments of 29 afforded the following coupling constant: $J_{3,5}=J_{2,5}=0.6$ Hz, $J_{2,3}=1.1$ Hz and $J_{2,6}=0.4$ Hz. The small J value between H_2 and H_3 indicates an almost 90° dihedral angle and, hence, a trans orientation for the CO_2CH_3 and CO_2H functionalities. The observed long range couplings $J_{2,5}$, $J_{3,5}$ and $J_{2,6}$ indicated the "W" or "zigzag" requirement for four-bond and five-bond coupling must be operative. The structure depicted in 29 best fits the observed coupling data. Compounds 28 and 29 showed only weak antibacterial activities against gram positive strains.





19, X = Y = CO_2CH_3, R = OH

20, X = Y = CO_2CH_3, R = Cl

21, X = CO_2CH_3, Y = CO_2pNB, R = OH

22, X = CO_2CH_3, Y = CO_2pNB, R = Cl

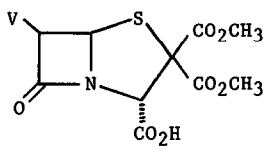
23, X = Y = SO_2CH_3, R = OH

24, X = Y = SO_2CH_3, R = Cl

25, X = Y = CO_2CH_3

26, X = CO_2CH_3, Y = CO_2pNB

27, X = Y = SO_2CH_3



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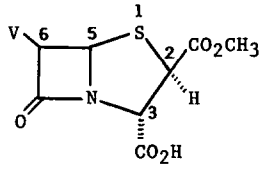

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In addition to 2-modified penams such as those prepared herein, the intermediates obtained from carbon nucleophilic displacement reactions on Kamiya's azetidinone should allow the preparation of a variety of novel β-lactam-containing structures. These studies are currently in progress in this laboratory.

Acknowledgement

We wish to thank the Analytical Research Department for the nmr decoupling experiments, and the Microbiology Research Department for the antibacterial assays.

References and Notes

1. Kamiya, T; Teraji, T; Saito, Y; Hashimoto, M; Nakaguchi, O. Tetrahedron Lett. 1973, 3001.

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6. This compound has been reported. Brain, E. G; Eglington, A. J; Nayler, J.H.C; Osborne, N, F.; Southgate, R. J. Chem. Soc. Perkin I, 1977, 2479.

7. Attempted hydrogenation of 27 yielded only degraded material.

8. All new compounds had spectroscopic properties consistent with the assigned structrues.

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