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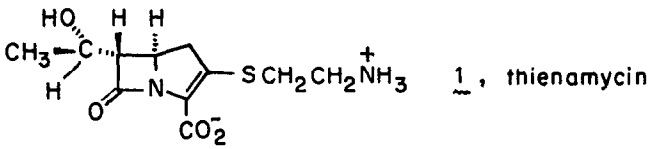
CYCLIZATION REACTIONS OF 4-(3'-BUTENYL)AZETIDIN-2-ONE A ROUTE TO THE CARBOPENAM RING SYSTEM

Tetsuo Aida, Richard Legault, Denise Dugat and Tony Durst
Department of Chemistry, University of Ottawa
Ottawa, Canada, K1N 9B4

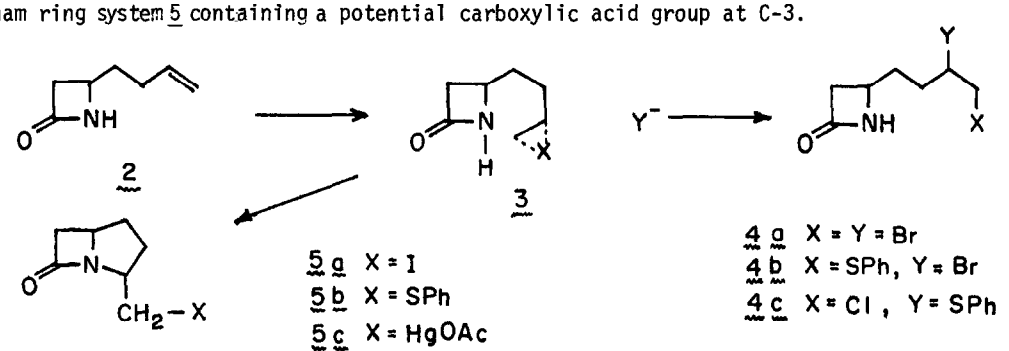
ABSTRACT: Cyclization of 4-(3'-butenyl)azetidin-2-one, 2 initiated by electrophilic reagents such as I_2, $Hg(OAc)_2$ results in the formation of bicyclic β-lactams having the carbopenam ring skeleton. Reaction of 2 with Br_2 results in simple addition of Br_2 to the double bond, while PhSBr gives a mixture of cyclization and addition products.

The recent discovery of the potent antibiotic thienamycin 1[1] has prompted us to search for an efficient synthesis of bicyclic β-lactams having the thienamycin ring skeleton which might be of value in the synthesis of 1, dihydro 1, or derivatives thereof. In this communication we report initial results in our study.



1, thienamycin

The title monocyclic β-lactam 2 was considered to be a key starting material since cyclization initiated by an electrophilic reagent as outlined below would lead to the carbopenam ring system 5 containing a potential carboxylic acid group at C-3.



5a X = I
5b X = SPh
5c X = HgOAc

4a X = Y = Br
4b X = SPh, Y = Br
4c X = Cl, Y = SPh

Compound 2[2,3] was obtained in 75% yield via a 14 day room-temperature reaction between chloro-sulfonyl isocyanate and 1,5-hexadiene in CH_2Cl_2 containing anhydrous Na_2CO_3, followed by reduction of the intermediate N-chlorosulfonyl β-lactam with $Na_2S_2O_3$.[4]

Reaction of 2 with Br_2 or pyridinium bromide perbromide in CH_2Cl_2 at 0° or at -78°, or in water-methanol at 0-25° gave only the 1,2-adduct 4a[2,5]. Presumably Br is a better nucleophile than the internal amide nitrogen in the trapping of the bromonium ion in 3.

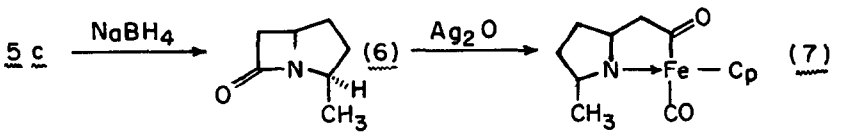
In contrast, reaction of 2 with I_2 in CH_2Cl_2 containing anhydrous Na_2CO_3 afforded in 62% isolated yield the bicyclic iodide 5a (X-I)[2]. The structure assignment of 5a was based on its i.r. spectrum (1760 cm^{-1}); ^1H nmr and ^{13}C nmr[6]. The latter was particularly informative, showing only seven signals including one at δ = 4.4 which is typical of a CH_2I carbon[7]. Interestingly, only one isomer appears to be formed in this cyclization as judged by the nmr

spectra of both the crude and purified products.

Cyclization of 2 to 5b(X = SPh) was also observed, albeit to only a small extent, using PhSBr as the electrophilic reagent. In this reaction, the Markownikoff addition product 4b, (X=Br, Y=SPh) was obtained as the major product (80%). Two cyclization products were also obtained. The more polar one, isolated in 10% yield was assigned the structure 5b, since it was identical to the product obtained in 90% yield from the reaction of 5a with LiSPh in THF[8]. The second cyclization product appeared to be an isomeric mixture of a 4,6-fused ring system; its structure has not been unambiguously established.

Other phenylsulfenyl halides gave even smaller amounts of cyclization products on reaction with 2. For example, PhSCl and 2 when reacted in CH_2Cl_2 at -78°, gave almost exclusively the anti-Markownikoff product 4c, while PhSI generated *in situ* from PhSSPh and I_2 afforded a mixture of products consisting of N-phenylsulfenyl-3(3'-butenyl)azetidin-2-one, the bicyclic sulfide 5b and the iodide 5a in a 65:12:23 ratio.

Efficient cyclization of 2 to 5c occurred with $Hg(OAc)_2$ in either THF-H_2O mixtures or in $CDCl_3$ solution. The organomercurial, obtained in virtually quantitative yield was characterized by its ^1H and ^{13}C spectra and reduction to 6 (75% overall) upon treatment with $NaBH_4$. Compound 6 was also obtained as a single diastereomer which had a proton nmr identical to the product obtained by Rosenblum and co-workers[9] from the oxidative cyclization of the iron carbonyl complex 7.



Further work on the cyclization of 2 to useful bicyclic systems, and additional modifications of 5 will be described in a full paper.

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REFERENCES

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2. All new compounds were characterized by m.s. and/or analysis. Infrared and nmr data were also in agreement with the proposed structures.
3. Nmr: ^1H; 1.5-2.4(m,4H), 2.57(ddd,J=12,2,1 Hz), 3.10(ddd, J=12,4,2 Hz), 3.4-3.5(m,1H), 4.8-6.3(m,3H), 7.2(bs,NH). ^{13}C; 30.6, 34.6, 43,4, 47,8, 115.5, 137.3, 168.6 Ir; 1745 cm^{-1}. b.p. 107-109° (0.35 Torr).
4. T. Durst and M.J. O'Sullivan, J. Org. Chem., 35, 2043 (1970).
5. Nmr: ^1H; 1.6-2.4(m,4H), 2.66(dd,J=12, 2 Hz), 3.16(ddd, J=12,4,2 Hz), 3.5-4.0(m, 3H), 4.1-4.4 (m, 1H), 7.5-7.9(bs, NH). ^{13}C; 32.6, 32.7, 35.8, 43.5, 47.3 and 47.4, 51.5 and 51.6 167.9, M^+ = 265.
6. Nmr: ^1H; 1.5-2.5(m, 4H), 2.63(dd,J=12,2 Hz), 3.00(dd,J=12,4 Hz), 3.0-4.1(m,4H). ^{13}C: 4.4, 29.5,27.6 42.8,53.1, 62.8, 167.7.
7. Carbon-13 N.M.R. Spectroscopy, J.B. Stothers, Academic Press, N.Y. 1972 Ch. 5.
8. Nmr: ^{13}C(non-aromatic peaks); 29.5,34.7,36.1,42.3,52.5,60.9,174.3. Ir. 1765 cm^{-1}.
9. P.K. Wong, M. Madhavarao, D.F. Marten and M. Rosenblum, J. Amer. Chem. Soc., 99, 2823, (1977), and privatecommunication from Prof. Rosenblum who assigned the exo-configuration to this compound.

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