A FACILE SYNTHESIS OF FUNCTIONALIZED NOVEL MONOCYCLIC TRANS- β -LACTAMS

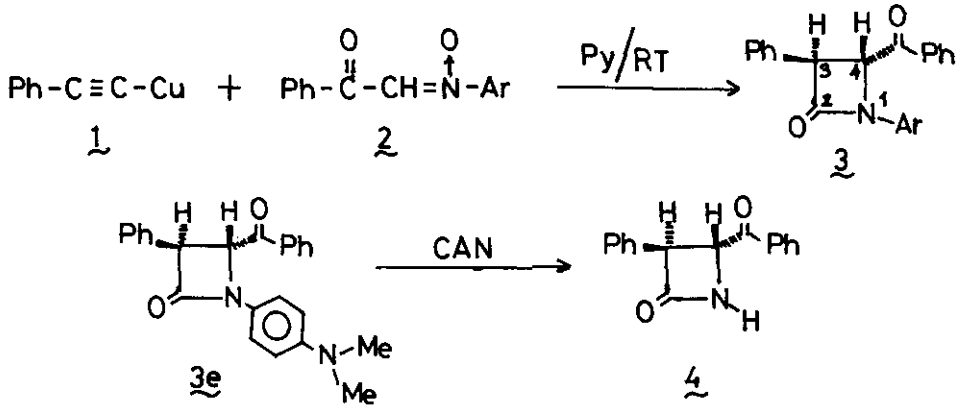
Dilip Kumar Dutta, Romesh Chandra Boruah, and Jagir Singh Sandhu*
Division of Drugs and Pharmaceutical Chemistry
Regional Research Laboratory, Jorhat 785 006, India

Abstract - Treatment of copper acetylide (1) with aroyl-N-aryl nitrone (2) afforded a novel class of 4-aroyl functionalized monocyclic trans- β -lactams (3). Oxidative N-dearylation of 3e with cerric ammonium nitrite (CAN) gave N-unsubstituted trans- β -lactam (4) in good yield.

Among the several antibacterial classes of compounds, the group of β -lactam antibiotics had been the major target of molecular manipulations[1,2]. The discovery of highly potent broad spectrum antibiotic thienamycin and monobactam has clearly revealed that the presence of 6-amido side chain and fused thiazole ring of β -lactam is not absolute requirement for biological activity[3]. Also despite intense work in this area there still remains much to be learned about the fundamental factors that influence their antibacterial action and in particular about the structural and conformational requirement for activity[4]. Several synthetic routes[5,6] for the preparation of monocyclic β -lactams and their conversion[7] to bicyclic or polycyclic β -lactams including naturally occurring hydroxypenams have been reported. The substituent at the 4-position of monobactam contributes substantially to the biological properties of β -lactams[8]. In this communication we wish to report a facile synthesis of monocyclic trans- β -lactam bearing a readily pliable carbonyl group at 4-position and conversion of the N-aryl substituted β -lactam to N-unsubstituted derivative via oxidative N-dearylation with CAN.

To a solution of copper acetylide (1) (prepared in situ[9]) in pyridine was added a solution of benzoyl-N-tolylnitrone[10] (2a) in pyridine at room temperature and the whole mixture was magnetically stirred overnight. After acidification, extraction with chloroform and subsequent workup afforded

trans-1-tolyl-3-phenyl-4-benzoylazetidin-2-one (3a) in 88% yield as the sole product, mp 190°C ; MS m/z 341 (M^+, 15%), 208 (100%), 133 (68%) ; IR ν_{max} (KBr) 1750 (C=O), 1695 (C=O) cm^{-1} ; ^1H NMR (100MHz, $CDCl_3$) δ : 2.31(s, 3H), 4.40(d, 1H, J=3Hz, H-3), 5.37(d, 1H, J=3Hz, H-4),7.15-7.89(m, 14H).



a Ar = p-CH_3-C_6H_4- b o-CH_3-C_6H_4- c p-Cl-C_6H_4- d C_6H_5- e p-$(CH_3)_2N$-C_6H_4-

Table

Compound	Yield %	Mp °C	IR ν_{max} cm^{-1}	^1H NMR ($CDCl_3$/TMS) δ ppm.	MS m/z (%)
3b	82	235-236	1750, 1695	2.40(s, 3H, 4.20(d, 1H, J=3Hz), 5.25(d, 1H, J=3Hz), 7.10-7.80 (m, 14H).	341(15), 208(100), 133(68).
3c	80	185-186	1750, 1695	4.28(d, 1H, J=3Hz), 5.37(d, 1H, J=3Hz), 7.10-8.10(m, 14H).	361(18), 228(100), 133(62).
3d	86	188-189	1750, 1695	4.28(d, 1H, J=3Hz), 5.37(d, 1H, J=3Hz), 7.27-7.93(m, 15H).	327(20), 194(100), 133(60).
3e	85	197-198	1745, 1690	2.90(s, 6H), 4.17 (d, 1H, J=3Hz), 5.17(d, 1H, J=3Hz), 7.20-7.90(m, 14H).	370(14), 237(100), 133(65).
4	80	227-228	3300, 1775, 1680	4.00(d, 1H, J=3Hz), 4.65(d, 1H, J=3Hz), 7.00-7.85(m, 11H).	251(35), 133(100), 118(45).

All the products gave satisfactory microanalytical data.

The configuration of the β-lactam ring was confirmed as trans arrangement on the basis of lower coupling constant values of H-3 and H-4 protons (3Hz) in NMR spectrum as the cis-β-lactam protons give higher values of coupling constants[11]. The support for the β-lactam structure to 3a is further enhanced by the characteristic mass spectral data where the molecular ion peak at m/z 341 is followed by fragmentation ion peak at m/z 208 (base peak) appeared due to the loss of isocyanate fragment (Ar-N=C=O). Similarly compounds (2b-e) reacted with (1) to give trans-β-lactam (3b-e) in excellent yields (Table). Attempted conversion of compounds (3a-d) with CAN in aceto-nitrile-water to N-unsubstituted β-lactam was unsuccessful. Only when azetidinone (3e) was employed N-dearylation in 80% yield was obtained.

ACKNOWLEDGEMENT

Authors are thankful to Prof. T. Kametani and Dr. T. Honda, Hoshi University, Tokyo 142, Japan, for providing IR, NMR and Mass spectral analysis of one of the products.

REFERENCES

1. a) Recent Advances in the Chemistry of β-Lactam Antibiotics. ed. by G.I. Gregory, Royal Society of Chemistry, London, 1981.
   b) Cephalosporin and Penicillins, Chemistry and Biology, ed. by E.H. Flynn, Academic Press, 1972.
   c) T. Kametani, N. Kanaya, T. Mochizuki and T. Honda, Heterocycles, 1983, 20, 435 and 455.
2. a) S. Wolfe, J-B Ducep, K.C. Tin and S.L. Lee, Can. J. Chem., 1974, 52, 3996.
   b) T.W. Doyle, B. Beleau, B-Yu. Luh, C.F. Farrari and M.P. Cunnigham, Can. J. Chem., 1977, 55, 468 and references cited therein.
   c) A.K. Mukherjee and A.K. Singh, Tetrahedron, 1978, 34, 1731.
   d) T.W. Doyle, B.D. Belleau, T.T. Conway, C.F. Farrari, D.E. Horning, G. Lim, B-Yu. Lua, A. Mortal, M. Menard and L.R. Morris, Can. J. Chem., 1980, 58, 2508.
   e) Recent Advances in the chemistry of β-Lactam Antibiotics, ed. by J. Elks, The Chemical Society, 1976.
3. a) G. Albers-Chorberg, B.H. Arison, O.D. Heusens, J. Hirstfield, K. Hooysteen, E.A. Kazeka, R.E. Rhodes, J.S. Kahan, F.M. Kahan,

R.W. Rateliff, E.A. Walton, L.J. Ruswinble, R.B. Morrin and B.G. Christensen, J. Am. Chem. Soc., 1978, 100, 6491.

b) J. Kahan, F. Kahan, E. Stapely, R. Gogelman and S. Hernandez, U. S. Patent, 1976, 3,950,357 ; Chem. Abstr., 1976, 85, 92190t.

4. D.D. Keith, J. Tengi, P. Rossman, L. Todro and M. Weigele, Tetrahedron, 1983, 39, 2445.

5. a) Chemistry and Biology of β-Lactam Antibiotics, Vol. 1, ed. by R.B. Morin and H. Gorman, Academic Press, New York, 1982.

b) M.D. Bachi and O. Goldberg, J. Chem. Soc., Perkin I, 1972, 2332.

c) M.D. Bachi and K.J. Ross-Peterson, J. Chem. Soc., Perkin I, 1975, 2525.

d) F.P. Cossio and C. Palomo, Tet. Lett., 1985, 26, 4235 and 4239.

e) B. Sain and J.S. Sandhu, Heterocycles, 1985, 7, 1611.

6. a) Y. Ohshiro, M. Komatsu, M. Vesaka and T. Agawa, Heterocycles, 1984, 22, 549.

b) G. Just and T.J. Liok, Can. J. Chem., 1978, 56, 211.

c) B. Sain, J.N. Baruah and J.S. Sandhu, J. Het. Chem., 1984, 21, 257.

7. Topics in Antibiotic Chemistry, Vol. 4, ed. by P.G. Summes, Ellis Harward Limited, New York, 1980.

8. C.M. Cimarusti, D.P. Bonner, H. Breuer, H.W. Chang, A.W. Fritz, D.M. Floyd, T.P. Kissik, W.H. Kloster, D. Kronenthal, F. Massa, R.H. Mueller, J. Pluscec, W.A. Slusarchyk, R.B. Sykes, M. Taylor and E.R. Weavers, Tetrahedron, 1983, 39, 2577 and references cited therein.

9. C.C. Bond and M.J. Hooper, J. Chem. Soc., C, 1969, 2453.

10. F. Krohnke and E. Borner, Ber., 1936, 69B, 2006 ; Chem. Abstr., 1936, 30, 6714.

11. S. Wolfe and W.S. Lee, J. Chem. Soc., Chem. Commun., 1968, 242.

Received, 22nd October, 1985