HETEROCYCLES, Vol. 29, No. 5, 1989

RING CONSTRUCTION OF BICYCLIC-β-LACTAM BY USE OF PALLADIUM CATALYZED CARBONYLATION

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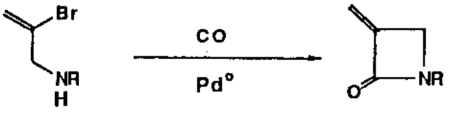
Abstract----Palladium catalyzed carbonylation into vinyl halide 10 afforded carbacepham 11 in good yield. The introduction of methoxycarbonyl group at C-4 position of carbacepham was achieved by conversion of methoxy group introduced by anodic oxidation in MeCN-MeOH to carboxyl group.

The search for β-lactam antibiotics possessing enhanced activity and resistance to β-lactamase has generated strong interest in methods of preparing the carbacephem and carbapenem skeletons. We have already reported the new synthetic method of α-methylene-β-lactams by use of palladium catalyzed carbonylation into 2-bromoallylamine derivatives.[1] This procedure prompted us to develope a new synthetic method of bicyclic β-lactam 5 from vinyl halide 4.



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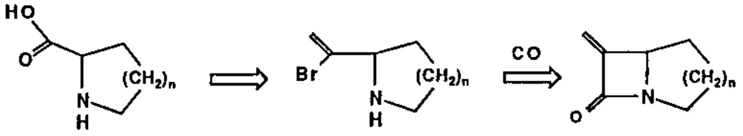

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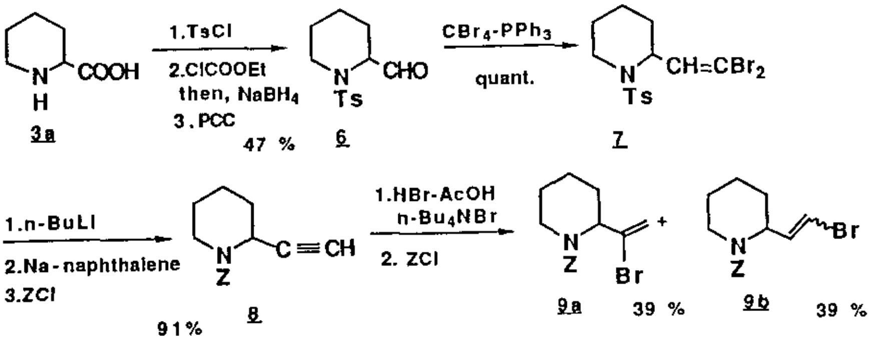
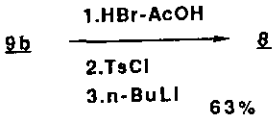
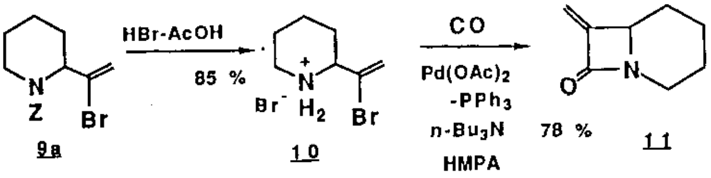
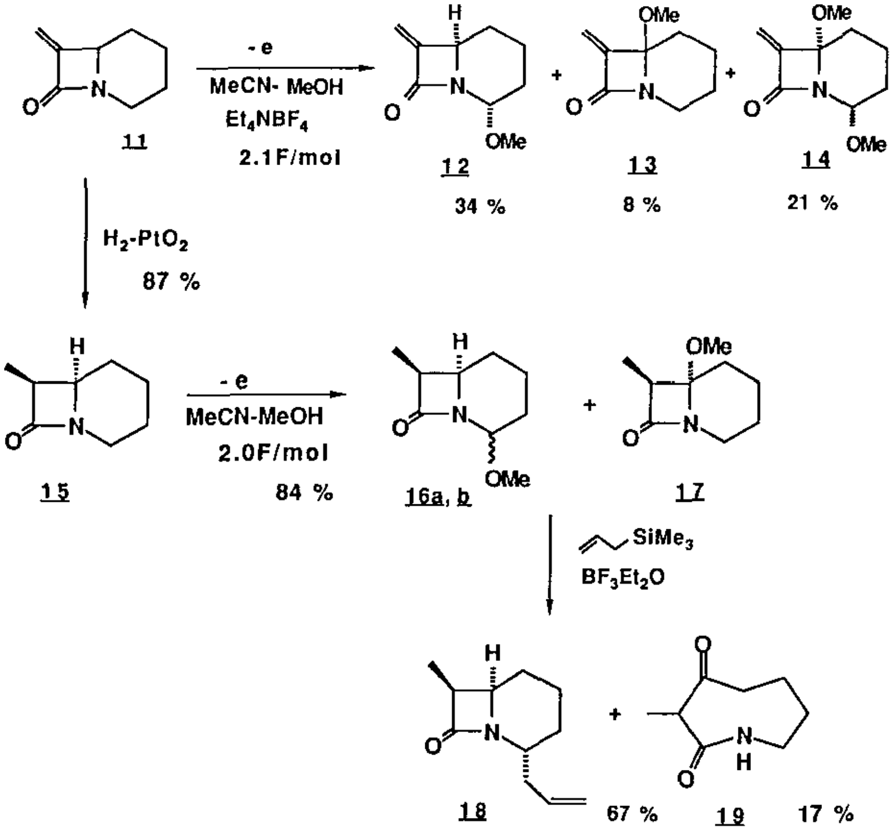
In order to prepare vinyl halide 4, the attempt to convert the carboxyl group of cyclic amino acid 3 such as proline(n=1) or pipecolinic acid(n=2), into vinyl halide was made. Pipecolinic acid 3a was converted to aldehyde 6 by usual method, which was treated with CBr_4-PPh_3 to afford vinyl dibromide 7. Treatment of 7 with excess n-BuLi[2] was followed by conversion of protecting group from tosyl group to benzyloxycarbonyl group[3]. Addition of HBr to compound 8[4] followed by protection of amino group with ZCl provided vinyl bromides, 9a and 9b in a ratio of 1 to 1. However,the latter vinyl halide 9b could easily give back to acetylene 8. Removal of the protecting group of 9a with HBr-AcOH afforded the desired vinyl bromide hydrogen bromide 10, which was successfully converted to bicyclic β-lactam 11 by palladium catalyzed carbonylation. Namely, a solution of vinyl halide 10, $Pd(OAc)_2$(2 mol %), PPh_3(4 mol %) and n-Bu_3N(2.5 eq) in hexamethylphosphoric triamide(HMPA) was heated at 100°C for 4 h under carbon monoxide(1 atm) to give β-lactam 11 in 78 % yield.



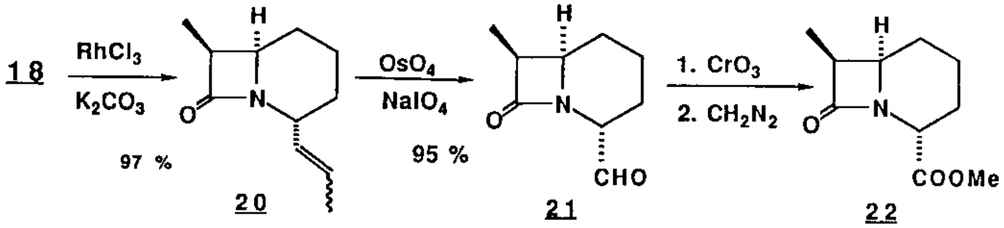




In order to introduce the carboxyl group at C-4 position of carbacepham 11, the anodic oxidation should be a suitable method because the methoxy group at the α-position of lactam[5] introduced by the anodic oxidation could be replaced by carbon nucleophile.[6] Thus, the electrochemical oxidation to β-lactam 11 was carried out in an undivided cell using platinum plates as electrode in MeCN-MeOH (9:1) containing Et_4NBF_4 as supporting electrolyte . After 2.1 F/mol of electricity was passed through the solution, methoxylated compounds 12, 13 and 14 were obtained in 34 %, 8 %, and 21 % yields, respectively.[7] Since the allylic position should be easy to oxidize for the electrolysis,[5b] α-methylene-β-lactam 11 was hydrogenated with PtO_2 to give compound 15 as a single product. The methyl group of compound 15 should be oriented to the β-position because the catalyst might approach from the less hindered site. When 2.0 F/mol of electricity was passed through the MeCN-MeOH(9:1) solution of compound 15, inseparable mixture of methoxylated compounds 16 and 17 was obtained in 84 % yield. The nmr spectrum indicated that the ratio of 16 to 17 was 7 to 1. Treatment of the mixture of 16 and 17 with allylsilane in the presence of BF_3Et_2O[8] gave compound 18 in 67 % yield along with compound 19 (17 % yield).[9] The latter compound 19 should be obtained from compound 17 by treatment with BF_3Et_2O in the presence of a small amount of water.



Compound 18 was treated with $RhCl_3$ in the presence of K_2CO_3 in EtOH followed by treatment with OsO_4 and $NaIO_4$ to give aldehyde 21 in good yield. Oxidation of compound 21 with CrO_3 provided carboxylic acid, which was converted into methyl ester 22[10] by treatment with CH_2N_2.



These results suggested that palladium catalyzed carbonylation into vinyl halide 10 afforded bicyclic β-lactam 11 in good yield. In order to introduce the carboxyl group at C-4 position of carbacepham skeletone, introduction of the methoxy group to the α-position of lactam by anodic oxidation was a good procedure because carbon nucleophile could be introduced to the methoxylated position. If proline was used for this reaction, carbapenam skeleton would be formed.

Further studies are in progress.

REFERENCES AND NOTES

1. M. Mori, K. Chiba, M. Okita, and Y. Ban, *Chem. Comm.*, 1979, 698 . M. Mori, K. Chiba, M. Okita, I. Kayo, and Y. Ban, *Tetrahedron*, **41**, 1985, 375 .
2. E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, 3769 .
3. The deprotection of the tosyl group with Na-naphthalene would accompany the debromination of vinyl halide.
4. J. Coussean, *Synthesis*, 1980, 805 .
5. a) M. Okita, T. Wakamatsu, and Y. Ban, *Chem. Comm.*, 1979, 749 . b) M. Okita, M. Mori, T. Wakamatsu, and Y. Ban, *Heterocycles*, **23**, 1985, 247 .
6. T. Shono, Y. Matsumura, and K. Tsubata, *J. Am. Chem. Soc.*, **103**, 1981, 1172 .
7. Compounds 12 and 13 were inseparable mixture, but the nmr spectrum indicated that compound 12 was a single isomer. Presumably, methoxy group should attack from the less hindered site of the acyl iminium cation generated by electrolysis.
8. G. A. Kraus and K. Neuenschwander, *Chem. Comm.*, 1982, 134 .
9. From the nmr spectrum of compounds 16 and 17, methoxylated compound 16 was a mixture of two isomers and the ratio of α-(16a) to β-methoxylated compound(16b) was 4 to 1. However, compound 18 was obtained as a single isomer.
10. Compound 22; ir ν_{max}(CHCl$_3$) 1730 cm^{-1}; ms m/e 197(M$^+$), 169(M$^+$-CO), 138(M$^+$-COOMe), 110, 82, 68, 55, high resolution mass spectrum Calcd for $C_{10}H_{15}NO_3$ 196.1069, found 196.1061; nmr δ(CDCl$_3$) 1.19(d, J=6Hz, 3 H), 1.4-2.2(m, 6 H), 3.4(m, 1 H), 3.74(s, 3 H, OMe), 3.8(m, 1 H), 4.56(bd, J=7 Hz, 1 H).

Recieved, 23rd January, 1989