Tetrahedron Letters,Vol.26,No.48,pp 5947-5950,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

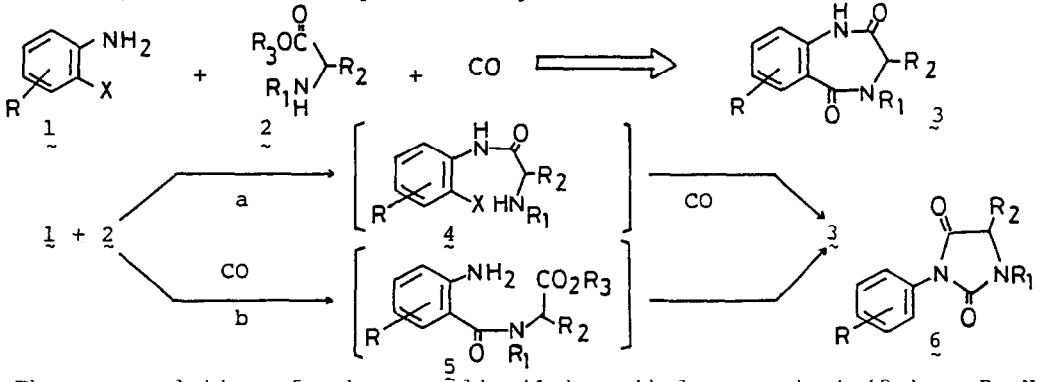
A ONE STEP SYNTHESIS OF 1,4-BENZODIAZEPINES: SYNTHETIC STUDIES ON NEOTHRAMYCIN

Miwako Mori, Masaya Kimura, Yasuhiro Uozumi and Yoshio Ban
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

(Dedicated to Prof. Harry H Wasserman on the occasion of his sixty-fifth birthday)

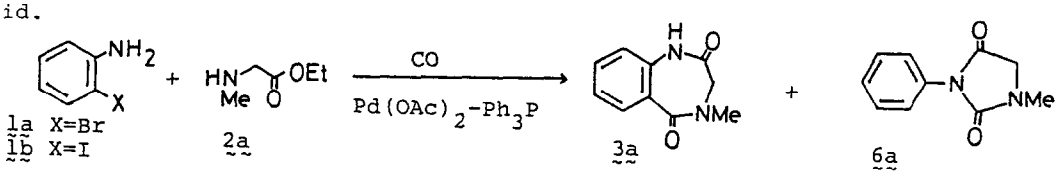
Summary: A one step synthesis of 1,4-benzodiazepines from o-haloanilines and amino acids was achieved by use of palladium catalyzed carbonylation, by which application a synthesis of the model compounds(23a and 23b) of Neothramycin (A and B) was described. An efficient chemoselective reduction of the amide was provided.

We have demonstrated the synthesis of 1,4-benzodiazepines by use of a palladium-catalyzed carbonylation.[1] In this method, the starting material was prepared from an o-haloaniline derivative and an amino acid. We have developed a one step synthesis of 1,4-benzodiazepines 3 by use of a palladium-catalyzed carbonylation from aryl halides 1 and amino acids 2. In this reaction, if the condensation of o-haloaniline and amino acid proceeds in preference to the Heck reaction,[2] the intermediate should be compound 4(route a). However, if the Heck reaction proceeds first, compound 5 should be the intermediate of this reaction (route b). We have already obtained hydantoin derivative 6 from compound 4 by use of palladium catalyzed carbonylation.[1c] In order to make a one-step synthesis of 1,4-benzodiazepines by use of the palladium-catalyzed carbonylation, the Heck reaction (route b) should proceed in prior to the condensation reaction.



Thus, a solution of o-bromoaniline(1a), methyl sarcosinate(2a), n-Bu_3N and a catalytic amount of $Pd(OAc)_2$-PPh_3 in HMPA was allowed to react under carbon monoxide(3 atm) at 110° for 3 days to afford a hydantoin derivative 6a in

27 % yield in addition to a small amount of 1,4-benzodiazepine 3a(Table 1, Run 1). The desired compound 3a predominanted over the hydantoin derivative 6a, when K_2CO_3 was used as a base instead of n-Bu_3N(Run 3 and 4). Methyl N-methyl-l-phenylalanate(2b) was used as an amino acid to afford l-cyclopeptine(3b) in one step, which is the metabolite of P. Cyclopium Westling,[3] but the yield was rather low. The reaction of methyl l-prolinate(2c) with o-iodoaniline(1b) and 2-bromo-4-methoxy-5-tosyloxyaniline(1c) gave pyrrolo-1,4-benzodiazepines 3c and 3d in moderate yields, respectively. Methyl pipecolinate(3d) afforded compound 3e in a similar manner. These results indicate that the one step synthesis of 1,4-benzodiazepines was achieved by use of the palladium catalyzed carbonylation from o-haloaniline and an amino acid.



1a X=Br
1b X=I

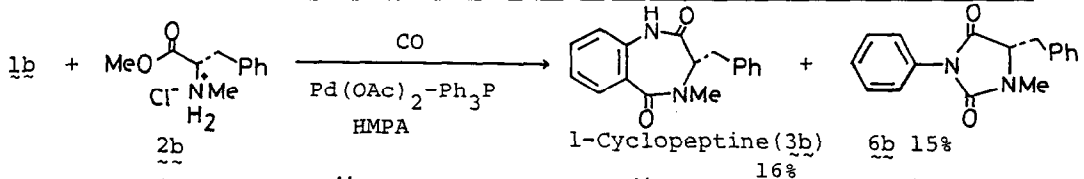
2a

3a

6a

Table 1 Palladium catalyzed carbonylation of o-haloaniline and 2a

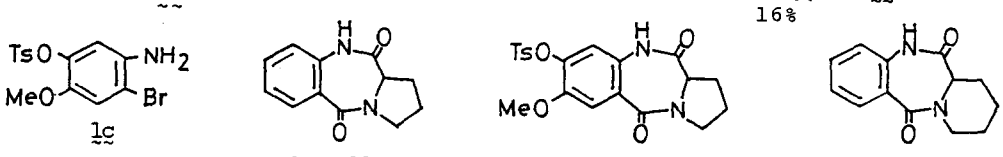
Run	X	Solvent	Base	3a	6a
1	Br	HMPA	n-Bu_3N	11 %	27 %
2	I	Xylene	n-Bu_3N	17	10
3	I	Xylene	K_2CO_3	33	-
4	I	HMPA	K_2CO_3	28	-



2b

l-Cyclopeptine(3b) 16%

6b 15%



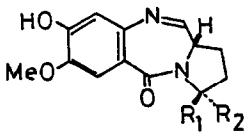
1c

3c 79%

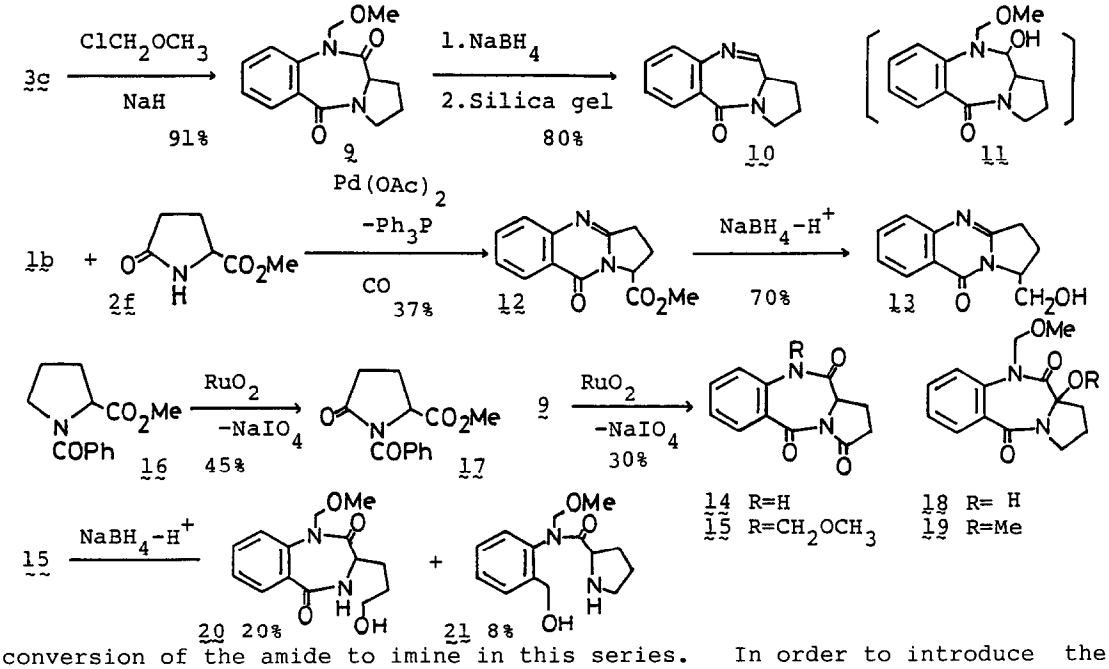
3d 41%

3e 18%

Neothramycin(7a and 7b) was isolated from a culture filtrate of Streptomyces No. MC916-C4 and exhibits a marked therapeutic effect on mouse leukemia L-1210 and Yoshida rat sarcoma.[4] For the total synthesis of neothramycin by our method, it was considered that compound 3d was a useful intermediate, though there were two problems. One of them was the reduction method of the amide group to an imino group[5] and the other was the introduction of the hydroxy group at the C-3 position. The former problem was solved by introduction of a methoxymethyl group to amide nitrogen. Compound 7 whose amide nitrogen was protected with the methoxymethyl group, was reduced with $NaBH_4$ in MeOH at 0°, followed by silica gel chromatography to give compound 10 in high yield(80 %), presumably, through the intermediacy of compound 11. This reducing technique might be recommended for selective

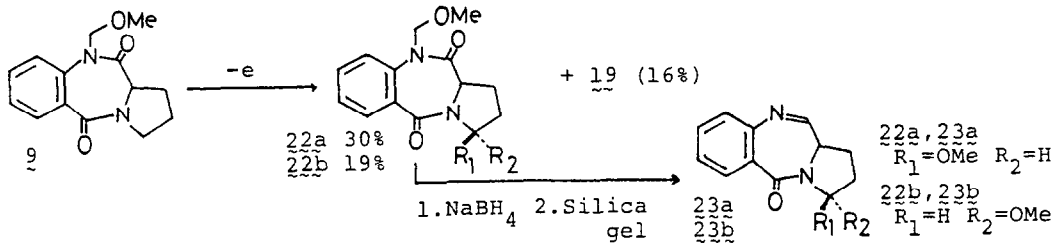


Neothramycin A; R_1=OH, R_2=H (7a)
Neothramycin B; R_1=H, R_2=OH (7b)
Methyl neothramycin A; R_1=OMe, R_2=H (8a)
Methyl neothramycin B; R_1=H, R_2=OMe (8b)



conversion of the amide to imine in this series. In order to introduce the hydroxy group at C-3 position, methyl pyroglutamate(2f) was chosen for the synthesis of the 1,4-benzodiazepine skeleton. However, a solution of o-iodoaniline(1b) and 2f was treated in the same manner to afford quinazoline derivative 12 instead of compound 14. The carbomethoxy group of compound 12 was converted to the hydroxymethyl group with $NaBH_4$ in the presence of acid. The structure of this compound was confirmed by ^{13}C-NMR spectra. Thus, an attempts was made to introduce the hydroxy group by oxidation of C-3 position. Oxidation of methyl N-benzoyl prolinate 16 with RuO_2-$NaIO_4$[6] afforded methyl N-benzoyl pyroglutamate 17 in 45 % yield along with the starting material(16, 36 %). The same treatment of compound 9 with RuO_2-$NaIO_4$ afforded compound 15 in addition to a small amount of 18. However, the selective reduction of imide 15 with $NaBH_4$ in the presence of acid[7] was unsuccessful affording compounds 20 and 21 in low yields.

We have already published that the anodic oxidation of N-alkyl-lactams in aq.CH_3CN or MeOH occurs regioselectively at the endocyclic carbon atom α to nitrogen in five and six-membered rings, and at the exocyclic α-carbon atom in seven-membered rings to provide hydroxy or alkoxy lactams.[8] Thus, the anodic oxidation of compound 9 using platinum plates as anode and cathode in an undivided cell in the presence of Et_4NBF_4 in 10 % MeOH-CH_3CN afforded the



desired compounds 22a and 22b in 30 % and 19 % yields, respectively, in addition to 19(16 % yield). The former compound 22a was reduced with $NaBH_4$ in MeOH at 0° followed by silica gel chromatography by the above method to afford 23a in 33 % yield along with the starting material (22a, 28 %). The latter compound 22b also gave compound 23b(36 % yield) and the starting material(22b, 58 %). The structure of these compounds were fully supproted by the spectral data(NMR, IR, MASS and High Resolution MASS). Comparson of the NMR spectra of compounds 23a and 23b with those of methyl neothramycins A and B(8a and 8b),[4] suggested that 23a should possess the β-alkoxy group. Neothramycins A and B(7a and 7b), which are interconvertible in a aqueous solution, are readily converted to methylneothramycin A and B(8a and 8b) in MeOH. Methylneothramycin A and B were easily converted to neothramycin A and B by mild hydrolysis with 0.01N HCl-dioxane[4]. These results mean that the compounds 23a and 23b possess the basic skeleton of Neothramycin A and B(7a and 7b).

Further studies on the total synthesis of neothramycin are in progress.

References and Notes

1. a) M. Mori, M. Ishikura, T. Ikeda and Y. Ban, Heterocycles, 16, 1491(1981). b) M. Ishikura, M. Mori, T. Ikeda, M. Terashima and Y. Ban, J. Org. Chem., 47, 2456,(1982). c) M. Mori, G.-E. Purvaneckas, M. Ishikura and Y. Ban, Chem. Pharm. Bull., 32, 3840 (1984).
2. Heck et al, reported the ingenious synthesis of primary and secondary amide from aryl halide and a primary and secondary amine by use of a palladium-catalyzed carbonylation. A. Schoenberg and R. F.Heck, J. Org. Chem., 39, 3327 (1974).
3. a) J. Framm, L. Nover, A. Azzouny, H. Richter, K. Winter, S. Werner, and M. Luckner, Eur. J. Biochem., 37, 78 (1973). b) A. Bracken, A. Pocker and H. Raistrick, Biochem. J., 57, 587 (1954). c) Y. Mohammed and M. Luckner, Tetrahedron Lett., 1953 (1963).
4. a)T. Takeuchi, M. Miyamoto, M. Ishizuka, H. Naganawa, S. Kondo, M. Hamada and H. Umezawa, J. Antibio., 29, 93 (1976). b) First total synthesis of Neothramycin was achieved by their group. M. Miyamoto, S. Kondo, H. Naganawa, K. Maeda, M. Ohno and H. Umezawa, ibid., 30, 340 (1977).
5. a) Recently, T. Kaneko et al, have reported the Al-Hg reduction of amide group to imino group of 1,4-benzodiazepines via imino thioether in a moderate yield and they succeeded in the total synthesis of chicamycin by their method. T. Kaneko, H. Wong, and T. W. Doyle, Tetrahedron Lett., 24, 5165 (1983). J. Antibio., 37, 301 (1984). b) D. E. Thurston, P. T. P. Kaumaya and L. H. Hurley, Tetrahedron Lett., 25, 2649 (1984).
6. a) J. C. Sheehan and R. W. Tulis, J. Org. Chem., 39, 2264 (1974). b) S. Yoshifuji, H. Matsumoto, K. Tanaka and Y. Nitta, Tetrahedron Lett., 2963 (1980).
7. J. B. P. A. Wigingberg, H. E. Schoemaker and W. N. Speckamp, Tetrahedron, 34, 179 (1978).
8. a) M. Okita, T. Wakamatsu and Y. Ban, J. C. S. Chem. Comm., 1979, 749. b) M. Okita, M. Mori, T. Wakamatsu and Y. Ban, Heterocycles, 23, 247 (1984).

(Received in USA 24 June 1985)