ONE POT SYNTHESIS OF QUINAZOLINE DERIVATIVES BY USE OF PALLADIUM CATALYZED CARBONYLATION

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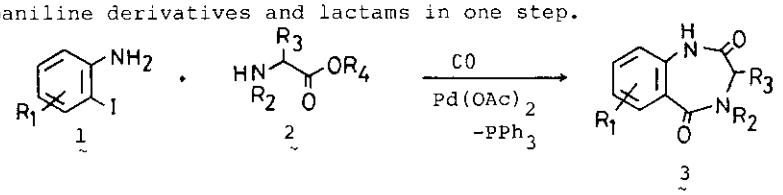
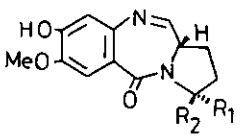
Abstract——One pot synthesis of quinazoline derivatives from a mixture of o-iodoaniline 1a and five membered lactams or N-acyl-o-iodoaniline derivatives, 1b and 1c, and primary amines was effected through the palladium-catalyzed insertion of carbon monoxide.

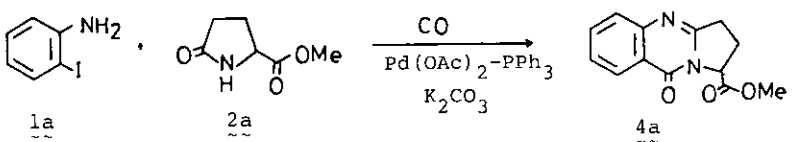
We have shown the one pot synthesis of 1,4-benzodiazepines from o-haloaniline derivatives and amino acid methyl esters by use of palladium catalyzed carbonylation.[1] During the course of the synthetic study of neothramycin by use of this method, quinazoline derivative 4a was obtained in a fairly good yield instead of compound 3a when methyl pyroglutamate 2a was chosen as amino acid. The intermediate of this reaction was considered to be compound 5 and the imide carbonyl carbon should be attacked by the amino group on the aromatic ring. These results suggested that quinazoline skeleton should be easily prepared from o-iodoaniline derivatives and lactams in one step.



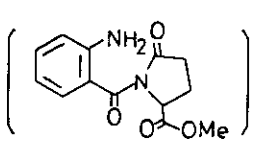
1 2 3



Neothramycin A; R_1=OH, R_2=H
B; R_1=H , R_2=OH



1a 2a 4a



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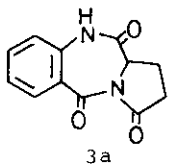
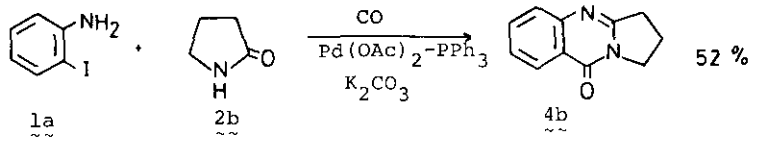
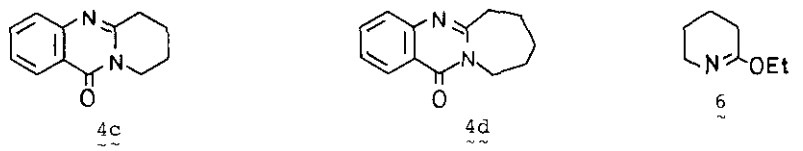
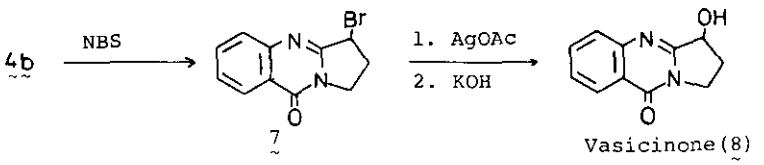


3a

Thus, a solution of o-iodoaniline, 2-pyrrolidone, K_2CO_3 and a catalytic amount of $Pd(OAc)_2$-PPh_3 in HMPA was heated at 110°C for 24 h under an atmosphere of carbon monoxide to afford compound 4b in 37 % yield. When 5 atm pressure of carbon monoxide was used in this reaction, the yield of quinazoline derivative 4b raised to 52 %. However, α-piperidone and ε-caprolactam gave compounds 4c[2] and 4d, only in 3 % yields, respectively. In order to increase the nucleophilicity of the lactam nitrogen, α-piperidone was converted to imino ether 6, but the yield of the desired compound 4c did not raise(7 %). Vasicinone(8),[3] isolated from Peganum harmala, was synthesized from compound 4b by modification of the Onaka's method.[4]

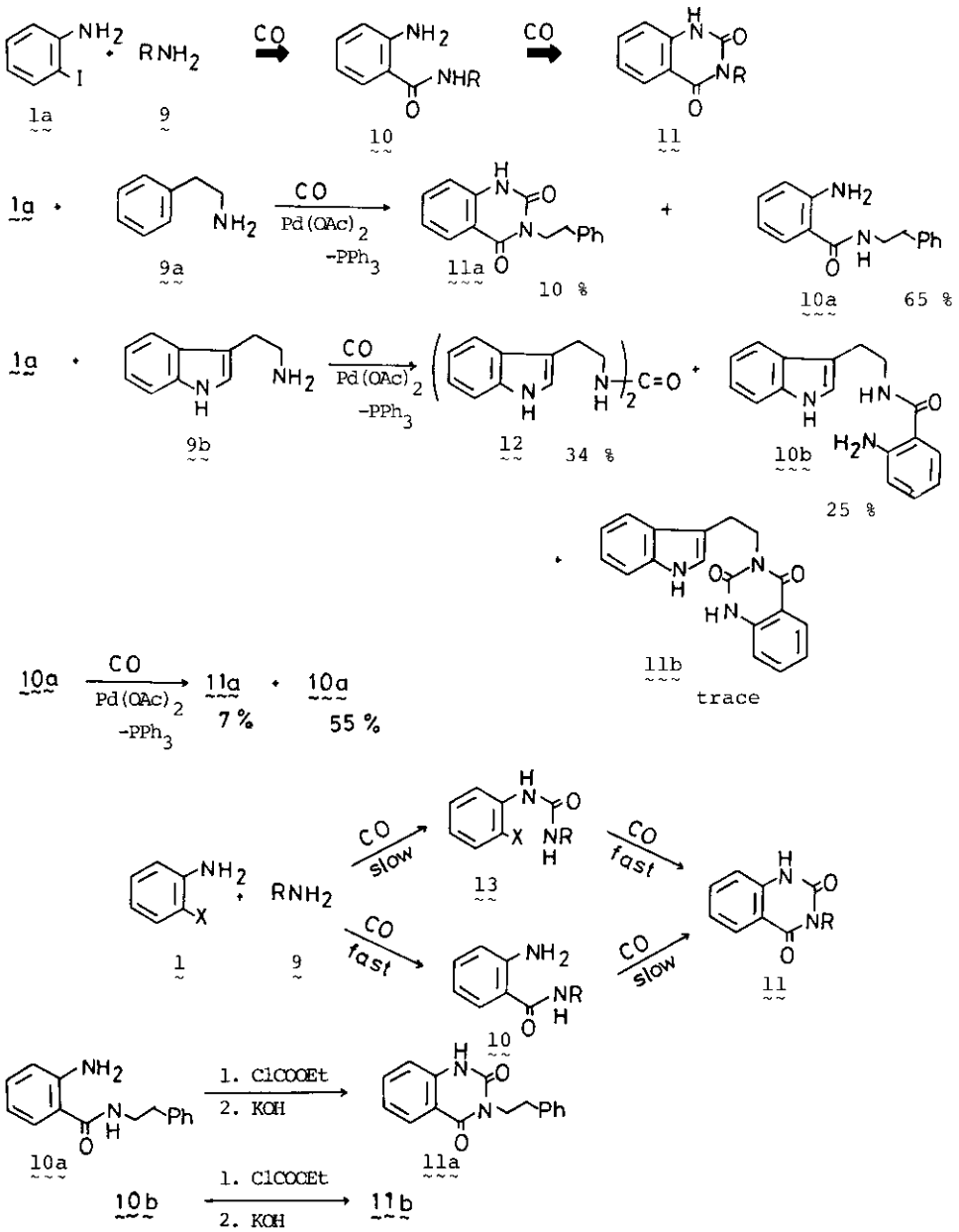




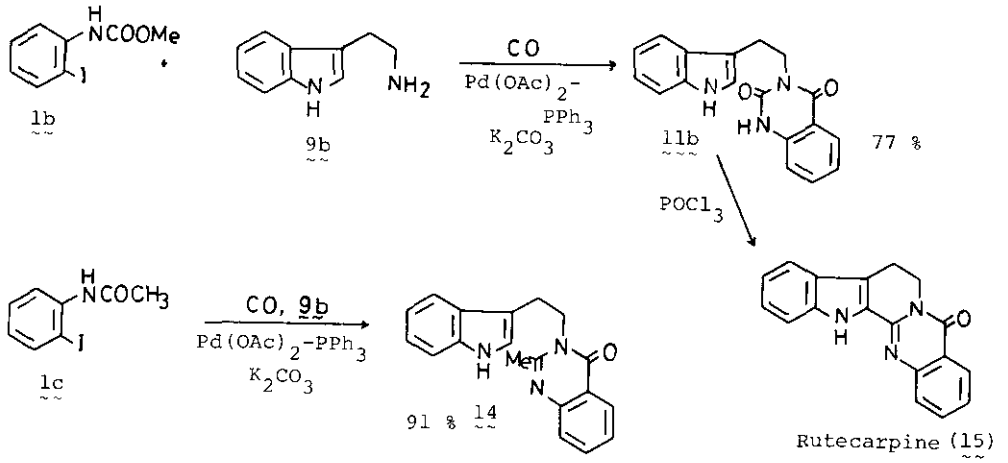


If o-iodoaniline was reacted with a primary amine in the presence of $Pd(OAc)_2$-PPh_3 under carbon monoxide, amide 10 should be formed(Heck reaction)[5]. Then if the insertion of carbon monoxide occurred between amide nitrogen and anilino nitrogen of 10, quinazoline derivative 11 should be formed.[6] Thus, a solution of o-iodoaniline(1a), β-phenethyl amine(9a), 10 mol % of $Pd(OAc)_2$-PPh_3 and K_2CO_3 in HMPA was allowed to react under carbon monoxide(5 atm) at 130°C for 72 h to afford the quinazoline derivative 11a and anthranilic acid derivative 10a in the yields of 10 % and 65 %, respectively. o-Haloaniline and tryptamine(9b) were treated in the same manner at 120°C for 24 h to afford compound 10b(25 % yield), urea derivative 12(34 % yield) and a small amount of the desired compound 11b. Since the anthranilic acid derivative 10 was considered to be an intermediate for the formation of the quinazoline derivative 11, compoumd 10a was treated with carbon monoxide in a similar manner, but the quinazoline derivative 11a was obtained in only 7 % yield along with the starting material(55 % yield). Thus a plausible reaction scheme was shown as follows. In this reaction, the formation of the urea derivative 13 should be slow compared with the formation

of the amide 10 and the insertion of carbon monoxide to the aryl halide and internal amide nitrogen of compound 13 should be fast because compound 13 was not formed in a detectable amount. However the insertion of carbon monoxide between the amide nitrogen and anilino nitrogen of compound 10 should be slow because a fair amount of the starting material 10 was recovered when the anthranilic acid derivative 10 was treated in a similar manner. Compounds 10a and 10b could be easily converted to quinazoline derivatives 11a and 11b by a known method.[7]



Subsequently, when N-carbomethoxy-o-iodoaniline(1b) and tryptamine(9b) were allowed to react with carbon monoxide(1 atm) at 120°C overnight, quinazoline derivative 11b was obtained in 77 % yield. N-Acetyl-o-iodoaniline(1c) was used as the starting material to form quinazoline derivative 14 in a high yield. Quinazolinocarboline alkaloid, rutecarpine(15),[8] which was isolated from the dried fruit of Evodia rutaecarpa by Asahina,[8a] could be synthesized from compound 11b by treatment with $POCl_3$ in dichloroethane at 60°C for 3 h in a yield of 40 % along with the starting material(27 % yield). It means that rutecarpine could be synthesized in only 2 steps from tryptamine.
Further studies are in progress.



REFERENCES AND NOTES

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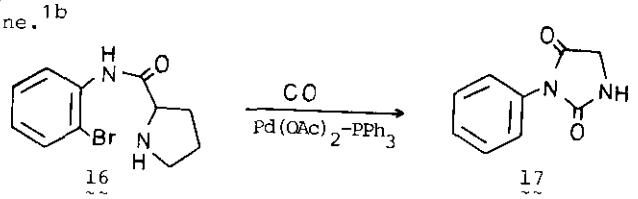
6. We have already obtained a hydantoine derivative 17 from o-haloaniline derivative 16 by the insertion of carbon monoxide between secondary amide and secondary amine.[1b]



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