A NEW SYNTHESIS OF 1,4-BENZODIAZEPINE BY THE PALLADIUM CATALYZED CARBONYLATION.

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It has been already reported that the insertion of carbon monoxide into o-bromoaminoalkylbenzene gave benzolactams by using zero-valent palladium complex as catalyst.[1)]

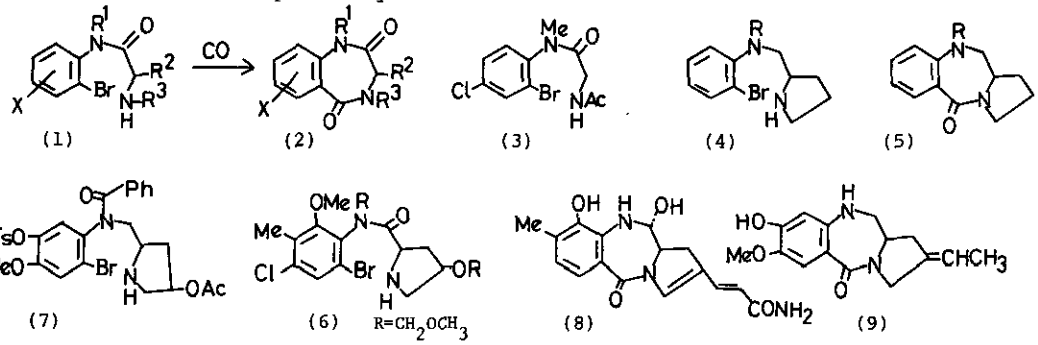
As an extension of this method, we now report a new synthetic route to 1,4-benzodiazepine(2) by the palladium catalyzed carbonylation of aryl halide(1) which was accessible by the condensation of o-bromoaniline with amino acid.

According to this method, diazepam, known as a sedative and hypnotic agent, was synthesized via aryl halide(3).[2)]

Moreover, the total synthesis of benzodiazepine bases, dehydrocyclopeptine, dl-cyclopeptine, dl-cyclopenin, and dl-cyclopenol, which were isolated from Penicillium cyclopium Westling and related moulds, was achieved by the present method.

Further exploration of this new synthetic method was effected for the synthesis of the more complex 1,4-benzodiazepine derivatives, pyrrolo-1,4-benzodiazepine antibiotics. In this case, utilization of aryl halide(4), which was obtained from o-bromoaniline and proline, was advantageous. The insertion of carbon monoxide into aryl halide(4) yielded pyrrolo-1,4-benzodiazepine(5).

This approach was also applied to the synthesis of anthramycin(8) and SEN-215(9) via aryl halide(6) and (7), respectively.



References: 1) M. Mori, K. Chiba and Y. Ban, J. Org. Chem., 43, 1684(1978). 2) M. Mori, M. Ishikura, T. Ikeda and Y. Ban, Heterocycles, in press.