

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-bromo-aminoalkylbenzene gave benzolactams by using zero-valent palladium complex as catalyst.¹⁾

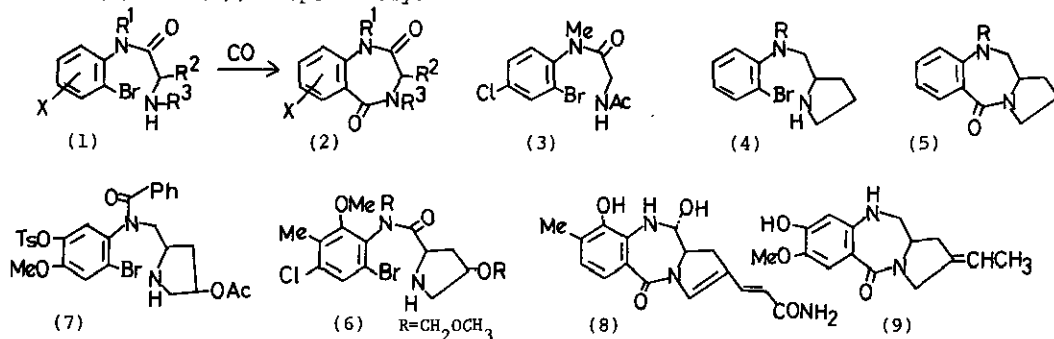
As an extension of this method, we now report a new synthetic route to 1,4-benzodiazepine(2) by the palladium catalyzed carbonylation of aryl halide(1) which was accessible by the condensation of o-bromoaniline with amino acid.

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, dehydrocycloheptine, dl-cycloheptine, dl-cycloheptenine, and dl-cycloheptenol, 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.