NEW SYNTHESIS OF DIAZEPINONE SKELETON USING PALLADIUM CATALYZED CARBONYLATION

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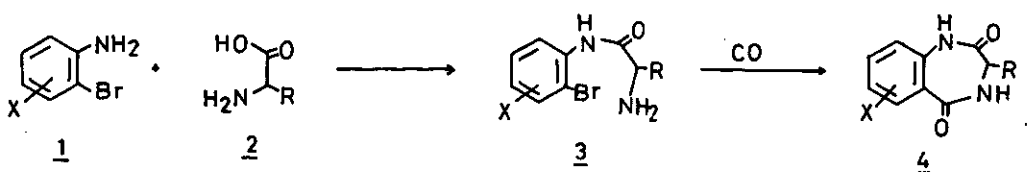
Abstract —— Palladium catalyzed carbonylation to the secondary amine(10) which was easily prepared from N-methyl-2-bromo-4-chloroaniline (1a) and carbobenzyloxyglycine(2a) gave 3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione derivative(11) in the yield of 30%. N-Acetyl derivative(14) of 8 was treated in the same manner to give the cyclic imide(15) in a fairly good yield and its result constitutes a new synthesis of diazepam(16).

Palladium catalyzed carbonylation to aryl and vinyl halides has been developed by us a very useful method for the synthesis of heterocyclic compounds, such as benzolactams,[1a] benzolactones[1b] cyclic imides,[1c] and α-methylene lactams and lactones.[1d] We have also achieved the synthesis of the natural alkaloids, sendaverine,[1e] and a formal synthesis of nocardicine A[1f] by application of this method.

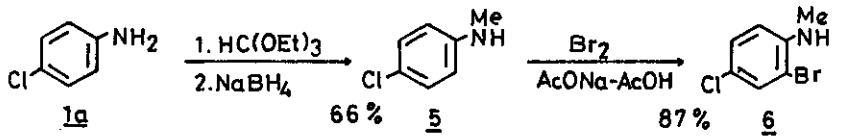
As is well known, 1,4-diazepine ring system constitutes a main part of diazepam and the related antibiotics.[2]

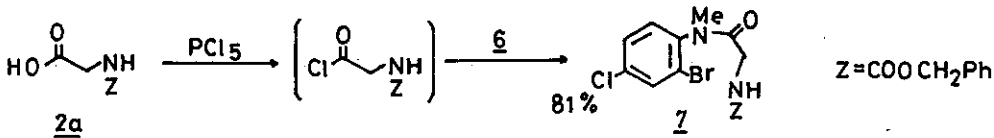
In this communication, the method has been extended to the synthesis of 3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione (4) by insertion of carbon monoxide into the aryl halides(3), which was readily prepared from o-bromoaniline derivative (1) and amino acid(2).

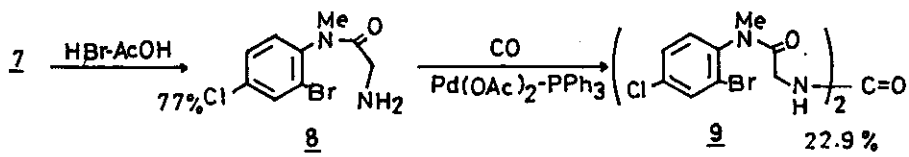


1 2 3 4

The starting material was commercially available p-chloroaniline, which was converted to N-methylated compound(5) by the known method.[3] Bromination of this compound(5) in the usual manner gave mono-brominated compound(6) in good yield, which was condensed with the acid chloride of carbobenzyloxyglycine obtained from 2a by treatment with PCl_5. The important intermediate(8) of this reaction was prepared by elimination of the carbobenzyloxy group from 7 with HBr-AcOH. Carbonylation of this compound(8) was carried out with 2 mol% of $Pd(OAc)_2$ and 20 mol% of PPh_3 in HMPA under 1 atm pressure of carbon monoxide at 100° for 26 h. However, the desired diazepinone derivative was not obtained, and instead only a small amount of the urea derivative(9, 22.9%) was generated.

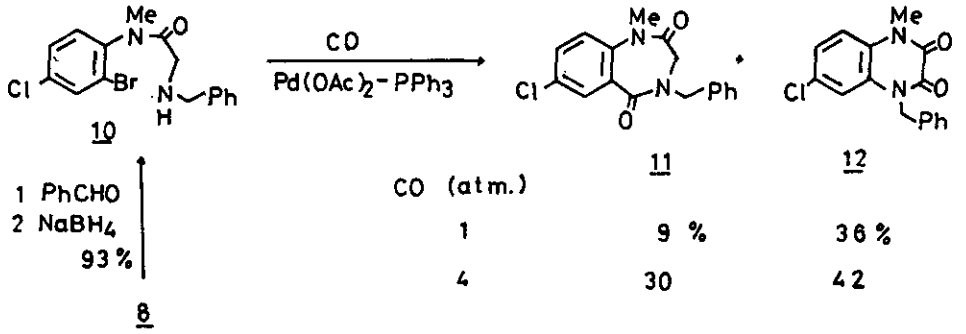


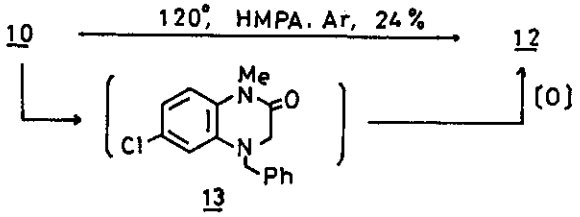


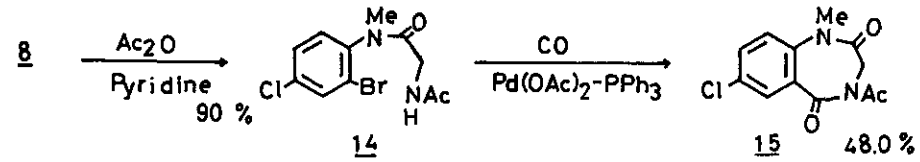


Subsequently, the secondary amine(10) which was prepared by condensation of the primary amine(8) with benzaldehyde, followed by reduction with $NaBH_4$, was reacted with carbon monoxide in the same manner to give a small amount of the desired compound(11, 9.0%)[mp 135-137°(from acetone-n-hexane); MS m/e 316, 314(M^+), 211, 209; IR νmax($CHCl_3$) 1675, 1640 cm^{-1}; NMR δ($CDCl_3$) 3.35(s, 3H, NCH_3), 3.75-3.80 (2H, $COCH_3$), 4.29(d, J=14Hz, 1H, PhCH), 5.39(d, J=14Hz, 1H, PhCH), 7.12(d, J=8Hz, 1H, aromatic), 7.28(s, 5H, aromatic), 7.48(dd, J=3, 8Hz, 1H, aromatic), 7.93(d, J=3Hz, 1H, aromatic)] and an unexpected product(12, 36.0%)[mp 241-242°(from acetone); MS m/e 302, 300(M^+), 209, 91; IR νmax(nujol) 1700, 1670 cm^{-1}; NMR δ($CDCl_3$) 3.69(s, 3H, NCH_3), 5.40(s, 2H, NCH_2Ph), 7.00-7.60(8H, aromatic)]. Afterwards, it was noticed that the tlc of the products conducted immediately after the reaction indicated two spots in addition to the spots of $PPh_3 \rightarrow O$ and HMPA. The

lower one was 11, but the higher one was unstable and changed during column chromatography on silica gel to the other stable one, which was proved to be 12. This compound was also obtained under the same condition without $Pd(OAc)_2$ in an argon atmosphere in 24.0% yield. Thus, it may be assumed that the condensation of the amino group with the halogen on the aromatic ring in 10 provided 13, which was oxidized during purification. When this reaction was carried out under 4 atm pressure of carbon monoxide, the yield of the desired diazepinone derivative(11) increased to 30.0% in addition to 12(42.0%).



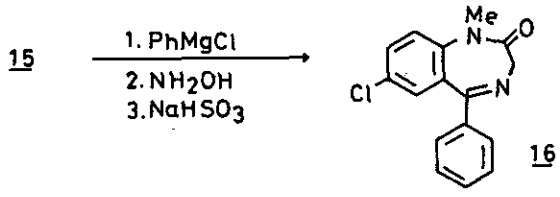




Since the aryl halide having amide group has been found by us to react with carbon monoxide to give the cyclic imide by this method,[1c] N-acetyl derivative(14) of the compound(8) was similarly heated with a catalytic amount of $Pd(OAc)_2$(10 mol%) and PPh_3(1 eq.) under 5 atm pressure of carbon monoxide at 100° for 40 h to give the desired cyclic imide(15) in the yield of 48.0%[mp 206-208°(lit.[4] 207.5-209°); MS m/e 268, 266(M^+), 253, 251(M^+-CH_3), 225, 223(M^+-COCH_3);

IR νmax(nujol) 1700, 1675 cm^{-1}; NMR δ($CDCl_3$) 2.67(s, 3H, $COCH_3$), 3.40(s, 3H, NCH_3), 3.50-4.00(m, 1H), 4.80-5.60(m, 1H), 7.23(d, J=9Hz, 1H, aromatic), 7.62 (dd, J=9, 2.5Hz, 1H, aromatic), 7.93(d, J=2.5Hz, 1H, aromatic)].

Recently, M. Gates has reported that diazepam(16) was obtained by reaction of this compound(15) with phenyl magnesium chloride followed by treatment of NH_2OH and then $NaHSO_3$.[4] Therefore, this result has provided a new synthesis of diazepam (16) by palladium catalyzed carbonylation for the generation of the compound(15).



Further studies of this reaction are in progress in this laboratory.

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References:

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