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Synthesis of 5-Oxo-L-Pipecolic Acid Derivatives by Rhodium(II) Acetate Catalyzed Cyclization of Diazoketones

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Key words : 5-Oxo-L-pipecolic acid ; Rhodium(II) acetate ; Diazoketone ; L-Glutamic acid ; N-H insertion

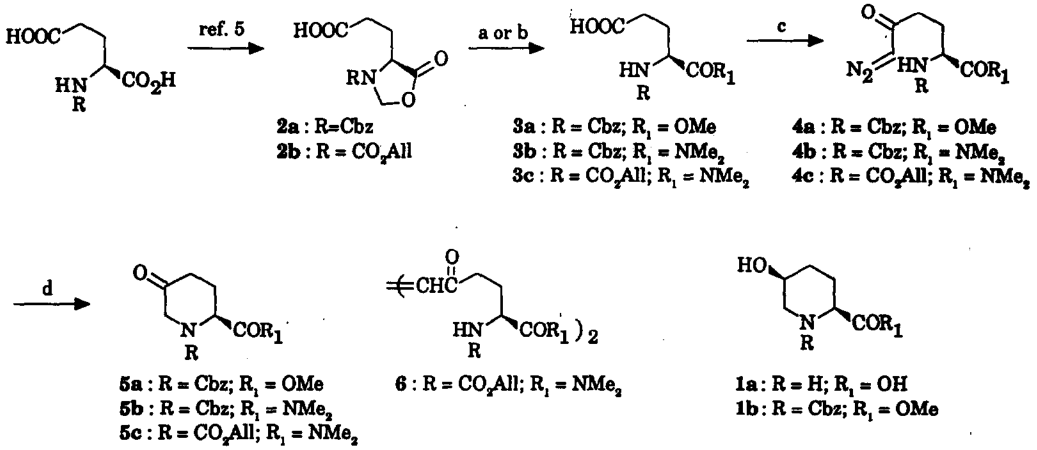
Abstract : *A convenient synthesis of 5-oxo-L-pipecolic acid derivatives is described. The key step involves the rhodium(II) acetate catalyzed N-H insertion reaction of diazoketones, which are derived from L-glutamic acid.*

cis-5-Hydroxy-L-pipecolic acid (**1a**, Scheme 1) is present in various plants such as Rhodesian teak, dates, and acacia.[1,2] Recently, a preparation of **1b** was reported, which as a key step involved a SN2-type cyclization of a chloroamine compound derived from L-glutamic acid. Reportedly, cyclization of α-chloroketone prepared from diazoketone **4a** to 5-oxo-L-pipecolic acid derivative **5a** was unsuccessful, presumably due to the reactivity of the carbonyl group.[2c] However, the one-step cyclization of **4a** to **5a** has not been yet reported.[3]

We have found that 5-oxo-L-pipecolic acid derivatives **5** can be easily prepared by the rhodium acetate catalyzed N-H insertion reaction of **4**, as shown in Scheme 1.[4]

Refluxing of the oxazolidinones **2a** and **2b** derived from L-glutamic acid[5] with 40% Me_2NH solution in water (ca. 3 molar equiv.) for 2 h gave the amides **3b** and **3c**, respectively.[6] Then, **3c** was converted to **4c** according to the known procedure[2c] (ClCOOEt, Et_3N, CH_2Cl_2 then CH_2N_2 at -5°C, 3 hr) in 62% yield after flash chromatography over silica gel (eluent : ethyl acetate/hexanes = 1/1), mp 92~93°C, $[\alpha]_D^{20} = +19.7°$ ($c = 1.93$, $CHCl_3$). Similarly, **4b** was prepared from **3b** in 70% yield by this procedure.

When **4c** was treated in CH_2Cl_2 (0.1 M solution) with a catalytic amount of rhodium (II) acetate (1% weight) for 3 h at room temperature, a separable mixture of polar product (**5c**, 39% yield), oil, $[\alpha]_D^{20} = +18.3°$ ($c = 2.65$, $CHCl_3$) and less polar product (**6**, 27% yield), mp 93~94°C, $[\alpha]_D^{20} = -106°$ ($c = 2.05$, $CHCl_3$) was obtained. It was found that the less polar portion was a dimer **6** as evidenced by mass spectroscopy (CI), *m/z* (relative intensity) 153 (25), 169 (10), 255 (100), 509 (M^+, 12). Also, ^1H NMR spectrum showed the presence of an olefinic proton (δ 6.16, singlet). It is remarkable that the dimer resulting from the intermolecular reaction is obtained in a considerable amount.[7] Cyclization in more dilute solution (0.01 M) suppressed the formation of the dimer and gave only the cyclized product in 30~40% yield after flash chromatography. In



Scheme 1. Reagents : a, NaOMe, MeOH; b, 40% aq. Me_2NH, H_2O; c, $ClCO_2Et$, Et_3N, CH_2Cl_2 then CH_2N_2-Et_2O, THF; d, cat. $Rh_2(OAc)_4$, CH_2Cl_2.

the rhodium acetate-catalyzed cyclization of **4c**, competition between N-H insertion and C-H insertion are possible.[4c] However, the formation of C-H insertion product was not observed in the present case. An attempted intramolecular C-H insertion of diazoketone derivative (DCC-CH_2N_2)[8] of **2a** was also unsuccessful. Similarly, **5a** and **5b** were prepared in 58 and 30% yields by the rhodium catalyzed N-H insertion reaction of **4a** and **4b**, respectively.

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