Tetrahedron Letters,Vol.29,No.52,pp.6917-6920,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

OXIDATIVE DECARBOXYLATION OF CYCLIC AMINO ACIDS AND DEHYDROGENATION OF CYCLIC SECONDARY AMINES WITH IODOSOBENZENE

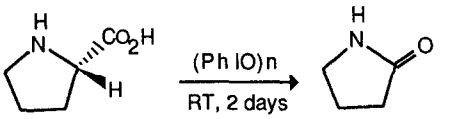
Masahito Ochiai,* Minako Inenaga and Yoshimitsu Nagao*
Institute for Chemical Research, Kyoto University
Uji, Kyoto-Fu 611, Japan

Robert M. Moriarty,* Radhe K. Vaid and Michael P. Duncan
Department of Chemistry, University of Illinois at Chicago
Chicago, IL 60680

Summary Cyclic amino acids L-proline, pipecolinic acid and L-2-pyrrolidinone-5-carboxylic acid undergo oxidative decarboxylation with iodosobenzene in various solvents (including water) to yield the lactam and imide in the latter case. The reaction proceeds *via* initial imine formation.

Oxidative decarboxylation of amino acids such as α-phenylglycine and phenylalanine with [bis(trifluoroacetoxy)iodo]benzene in the presence of pyridine has been reported to give the corresponding aldehydes, benzaldehyde and phenylacetaldehyde, respectively, in about 45% yield.[1] We find that oxidation of L-proline with iodosobenzene (ISB) yields 2-pyrrolidinone (1) under neutral conditions.

When L-proline was treated with 2.2 equiv. of ISB in dichloromethane at room temperature for 2 days, 2-pyrrolidinone (1) was obtained in 65% yield after chromatographic purification. The results are shown in Table 1. Interestingly, the oxidation may also be carried out in water (run 9, Table 1). In THF or methanol, the reaction gave a complex mixture of products. In chloroform the reaction afforded a 70% yield of (1). The use of excess ISB (5 equiv.) in dichloromethane led to the considerable decomposition of the product (1) and gave 2-pyrrolidone (1) in only 31% yield.



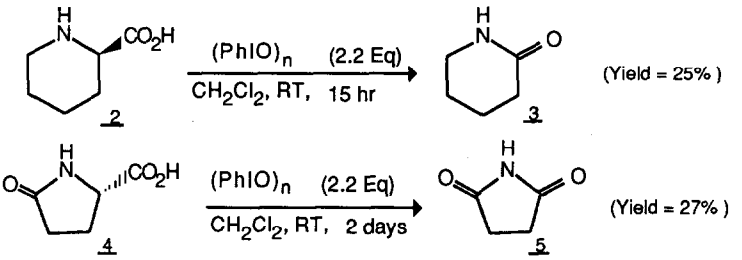
1

TABLE 1: Oxidative Decarboxylation of L-Proline to 2-Pyrrolidinone (1)

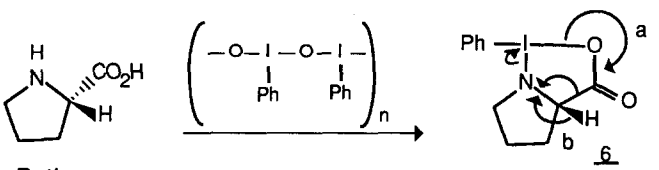
Run	Solvent	$(C_6H_5IO)_n$	Yield (%)
1	THF	2.2	complex mixture
2	MeOH	2.2	complex mixture
3	CCl4	2.2	11
4	MeCN	2.2	35
5	$CHCl_3$	2.2	70
6	CH_2Cl_2	2.2	65
7	CH_2Cl_2	3.3	56
8	CH_2Cl_2	5.0	31
9	H_2O	2.2	52

Similarly, oxidative decarboxylation of cyclic amino acids, pipecolinic acid (2) and L-2-pyrrolidinone-5-carboxylic acid (4) with $(PhIO)_n$ (2.2 Eq,CH_2Cl_2, RT) resulted in the formation of the corresponding lactam (3, 25%) and

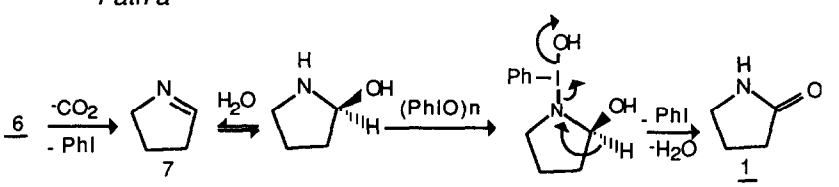
imide (5, 27%), respectively.



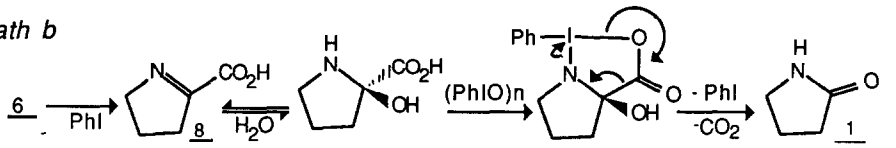
For the oxidative decarboxylation of cyclic acids, which requires 2 mol of ISB, the following two reaction pathways seem to be plausible. Path (a) involves a formation of 1-pyrroline (7), produced by the decarboxylation of the five-membered organoiodine (III) species (6). On the other hand, path (b) involves a formation of 1-pyrroline-2-carboxylic acid (8)[2] by dehydrogenation of L-proline through the same intermediate (6). In fact, dehydrogenation yielding imines took place when L-proline methyl ester (9) was oxidized with ISB (1.1 equiv.) in dichloromethane. The reaction afforded the methyl ester of (8) in 69% yield. The methyl ester (10) has been shown to be an important intermediate for the synthesis of (-)-detoxinine (11).[3]

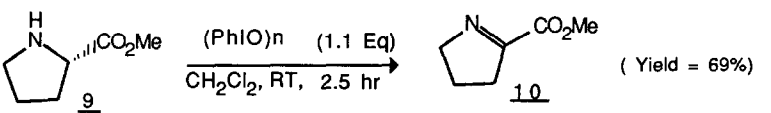


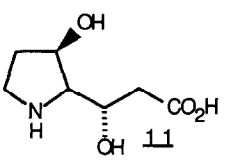
Path a



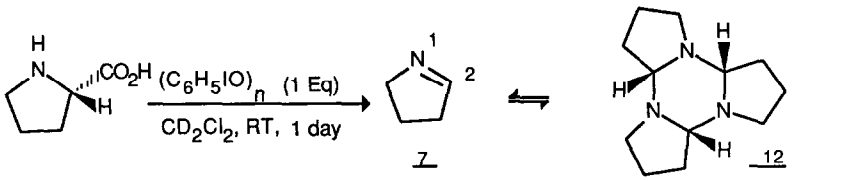
Path b



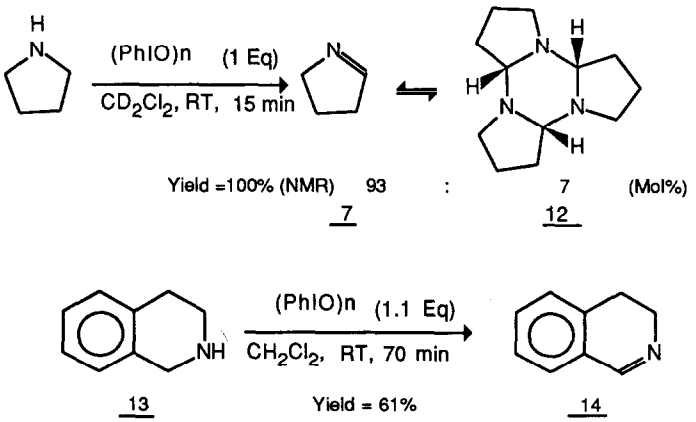


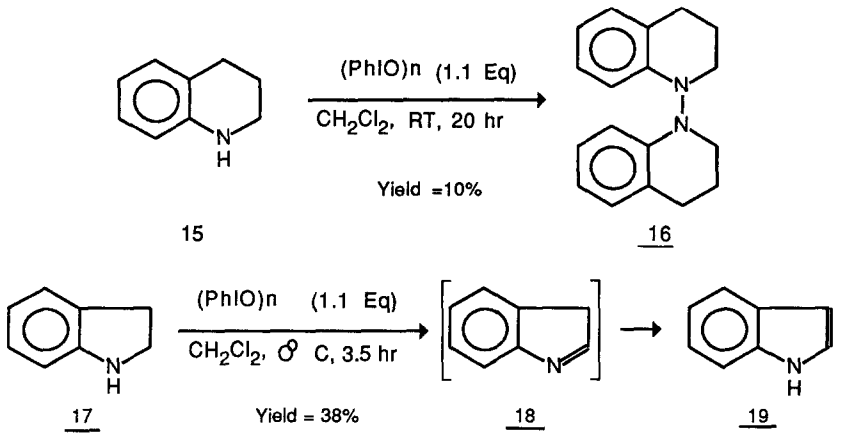


In order to distinguish between the oxidative decarboxylation pathway (a) and the dehydrogenation pathway (b), an NMR tube experiment of ISB oxidation of L-proline was carried out. Exposure of L-proline to one equiv. of ISB in dichloromethane-d_2 at room temperature for 24 hr resulted in the formation of a mixture of 1-pyrroline (7) and 1-pyrroline trimer (12). The yield was determined to be 94% by ^1H NMR and the ratio of (7): (12) was 94: 6 (mol%). In the ^{13}C NMR spectrum of the mixture, four peaks at δ 166.9 (d, C-2), 61.5 (t, C-5), 36.9 (t, C-3), and 20.8 ppm (t, C-4) were assigned to the monomer (7) and the other peaks at d 82.4, 46.1, 28.2 and 20.6 ppm were in good agreement with the reported value of the trimer (12).[4] 1-Pyrroline (7) is a labile compound and has never been isolated in the pure form. Coexistence of the monomer (7) and the trimer (12) at equilibrium in solution is well documented.[5] In methanol, the monomer (7) is a major component while in CCl_4 the trimer (12) is favored. The ratio obtained in this experiment does not necessarily reflect the equilibrium concentrations. Thus, these results clearly show that the oxidation of L-proline to 2-pyrrolidinone (1) by ISB should involve the formation of 1-pyrroline (7) as an intermediate. Further oxidation of (7) with another mol of ISB most likely explains the production of (1).



Dehydrogenation with ISB is not confined to L-proline methyl ester (9). Oxidation of pyrrolidine with one equiv. of ISB in dichloromethane at room temperature for 15 min afforded quantitatively a mixture of the monomer (7) and the trimer (12) in a ratio of 93: 7 (yield 100% NMR). Similarly, 3,4-dihydroisoquinoline (14)[6] was obtained from the oxidation ($(PhIO)_n$ 1.1 Eq, CH_2Cl_2, RT, 70 min.), of 1,2,3,4-tetrahydroisoquinoline (13) in 61% yield. 1,2,3,4-Tetrahydroquinoline (15), however, did not produce the desired 3,4-dihydroquinoline and underwent oxidative N,N-coupling reactions, yielding the dimer (16) (10% yield). Indoline (17) gave indole (19), probably produced *via* the isomerization of the dehydrogenation product (18), in 38% yield.





As in the case of the oxidation of cyclic amino acids, further oxidation of the imines, generated from cyclic amines, with a second mol of ISB led to the formation of the corresponding lactams, and this reaction is described in the accompanying paper.[7]

Acknowledgement: The American authors thank the U.S. Army for support of this work under contract DMAD 85-C-5190 and the Petroleum Research Fund PRF 17962.

References:

1. G.M. Loudon, A.S. Radhakrishna, M.R. Almond, J.K. Blodgett and R.H. Boutin, *J. Org. Chem.*, **49,** 4272 (1984).
2. M.V. Keenan and W.L. Alworth, *Biochem. Biophys. Res. Commun.*, **57,** 500 (1974).
3. W.R. Ewing, B.D. Harris, K.L. Bhat and M.M. Joullie, *Tetrahedron,* **42,** 2421 (1986).
4. a) Y. Nomura, K. Ogawa, Y. Takeuchi and S. Tomoda, *Chem. Lett.,* 693 (1977), b) K. Ogawa, Y. Nomura, Y. Takeuchi and S. Tomoda, *J. Chem. Soc., Perkin Trans. 1,* 3031 (1982).
5. a) H. Poisel, *Monatsh. Chem.,* **109,** 925 (1978), b) G.B. Edwards, K. Yamanouchi, K. Kuchitsu, M. Sugie, H. Takeo, C. Matsumura, K. Ogawa and Y. Takeuchi, *J. Mol. Spectrosc.,* **111,** 301 (1985).
6. S. Murahashi, T. Naota and H. Taki, *J. Chem. Soc., Chem. Commun.,* 613 (1985).
7. R.M. Moriarty, R.K. Vaid, M.P. Duncan, M. Ochiai, M. Inenaga and Y. Nagao, Submitted *Tetrahedron Letters* as an accompanying communication.

(Received in USA 28 July 1988)