Tetrahedron Letters No. 22, pp 1923 - 1926, 1978. 0040-4039/78/0522-1923$02.00/0

OXIDATIVE DECARBOXYLATION OF NITROSOAMINO ACIDS: A SYNTHETIC APPROACH TO CYCLIC α-ACETOXYNITROSAMINES

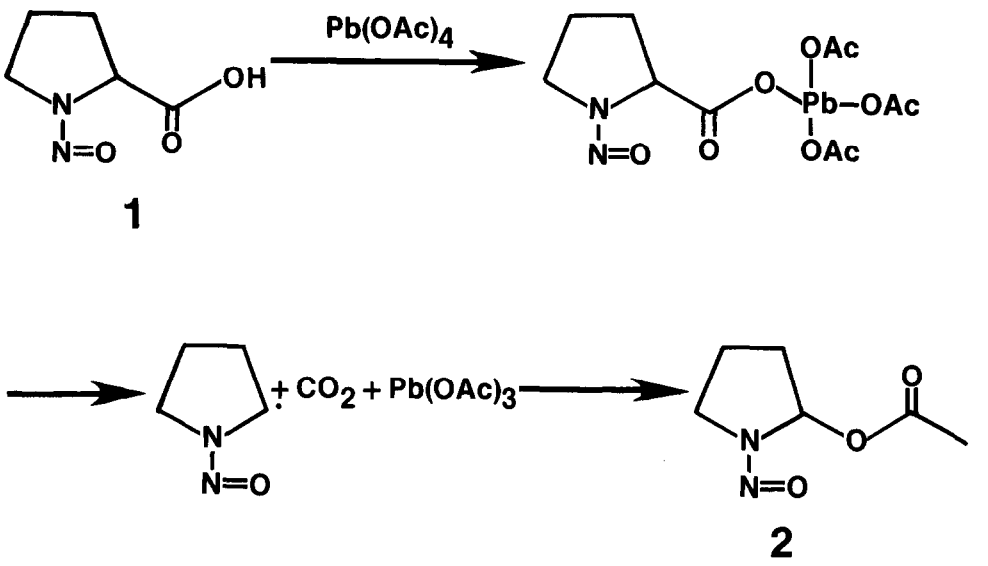
Jose E. Saavedra
NCI FREDERICK CANCER RESEARCH CENTER, Frederick, MD 21701 U.S.A.

(Received in USA 20 December 1977; received in UK for publication 3 April 1978)

Nitrosamines exhibit carcinogenic activity after metabolic activation by oxidizing enzyme systems[1]. This metabolic activation probably involves the replacement of a hydrogen group by an oxygen function[2], and these highly reactive oxygenated species could form a hydroxyazo intermediate which, upon loss of nitrogen, becomes an alkylating moiety. Support for this α-hydroxylation theory is found in the isolation of alkylated nucleic acid bases from tissues of animals treated with acyclic nitrosamines[3]. However, no alkylated purine bases[4] could be identified in the nucleic acid of rats treated with alicyclic nitrosamines such as nitrosoacetidine, nitrosopyrrolidine, and nitrosohexamethylenimine.

It has been difficult to provide evidence for α-hydroxylation of cyclic nitrosamines because relatively few compounds at this oxidation state are available. Synthetic methods for the formation of acyclic α-acetoxy nitrosamines are well established[2,5,6]. The first general method for the preparation of a cyclic α-acetoxynitrosamine was reported by J. Baldwin, et al.[7], who used nucleophilic displacement of the chloride ion[6] from α-chloro nitrosopyrrolidine by acetoxy group. Hecht et al.[8] have prepared two α-acetoxylated isomers of nitrosonornicotine using Baldwin's method.

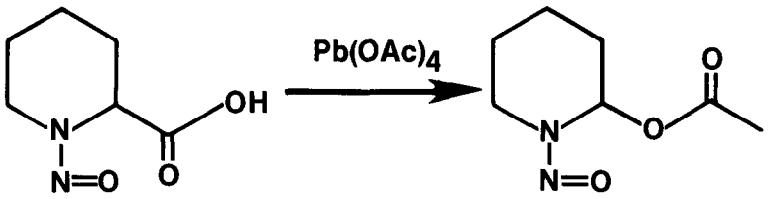
We report here our preliminary studies on the one-step syntheses of α-acetoxy nitrosopyrrolidine 2, and α-acetoxy nitrosopiperidine 4 by the oxidative decarboxylation of the corresponding nitrosoamino acids with lead tetraacetate. N-Acetylamino acids react with lead tetraacetate in dimethylformamide to produce acetamide, carbon dioxide and the corresponding aldehyde[9]. On the other hand, N-benzyl-, and N-benzoyl-glycine react to give the corresponding acetates[10]. It seems that this reaction applied to nitrosoamino acids might provide a route for synthesis of the proximate carcinogens. Therefore, the reaction of nitrosoproline 1 with lead tetraacetate might be expected to form a lead (IV) carboxylate which would decompose to an alkyl radical, and lead (III) acetate, followed by an oxidative elimination to an olefin or a substitution process as shown in scheme I[11].



SCHEME I

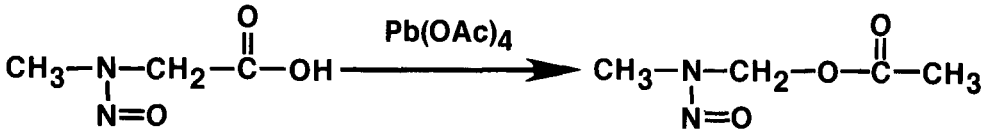
Nitrosoamino acids 1 and 4 were obtained in good yield from the corresponding amino acids using the method of Lijinsky et al.[12]. Compound 1 was dissolved in degassed dichloromethane containing 1.2 equivalents of anhydrous pyridine then treated with 1.2 equivalents of lead tetraacetate and stirred at room temperature under nitrogen for 19 hours. Yields of 35-44% were obtained under these conditions. Increasing the reaction time or raising the temperature did not improve the yield; in fact more by-products were obtained. The product mixture was analyzed by gas liquid chromatography (GLC) on a 1% QF-1 on chromosorb Q column (8',2" long) at 110°C with a helium flow rate of 60 ml per minute. The structure of the major component was shown by GLC-MS to be α-acetoxy nitrosopyrrolidine (m/e 158, 6.93%), (m/e 69, 100%). The base peak corresponds to the loss of the nitroso and the acetoxy groups. The crude product was vacuum distilled without significant decomposition[13]; nmr ($CDCl_3$): δ2.0-2.3 (m,4H), δ2.09 (s,3H), δ3.3-3.8 (m,2H), δ7.2-7.3 (m,1H); IR (film) 1745 cm^{-1}, 1450 cm^{-1}, 1370 cm^{-1}, 1225 cm^{-1}. The spectral properties of 2 are consistent with those reported by Baldwin[7].

Nitrosopipecolic acid 3 in methylene chloride and pyridine reacted with lead tetraacetate at room temperature to give 4 in 7-13% yield. When the reaction was carried out in benzene containing 1.2 equivalents of anhydrous potassium carbonate, the yield was 19-21%. The crude product was purified by column chromatography (Silica-gel). Mass Spectrum: m/e 172 (3.58%), m/e 143 (2.17%), m/e 113 (16.77%), m/e 83 (65.52%), m/e 55 (100%); IR (film) 1745 cm^{-1}, 1450 cm^{-1}, 1370 cm^{-1}, 1235 cm^{-1}; nmr ($CDCl_3$) δ7.3 (b,1H), δ4.80 (m,1H), δ2.66 (m,1H), δ2.06 (s,3H), δ1.2-2.2 (m,6H).



3 4

To demonstrate that this method could also be applied to the preparation of acyclic α-acetoxy nitrosamines, nitrososarcosine 5 was reacted with lead tetraacetate in methylene chloride containing 1.2 equivalents of pyridine. The 37% yield of methyl(acetoxymethyl) nitrosamine 6 was a considerable improvement over that previously reported[2,6].



5 6

Only a few secondary amino acids are commercially available. However, through carboxylation of lithio nitrosamines with carbon dioxide[14] a large variety of nitrosoamino acids can be prepared. The oxidative decarboxylation described in this paper may prove to be a general reaction for the formation of cyclic α-acetoxynitrosamines. CAUTION! α-acetoxynitrosamines may be direct-acting carcinogens. These compounds must be considered hazardous chemicals and precautions to avoid their release in the laboratory or the environment must be observed.

ACKNOWLEDGEMENT

This work was sponsored by the National Cancer Institute under Contract Number NO1-CO-25423, with Litton Bionetics, Inc. We wish to thank Dr. David Wilbur for the NMR spectra, and Mr. Sam Huang for recording the mass spectra.

REFERENCES

1. D.F. Heath, Biochem. J., 85, 72 (1962); F.W. Krüger, B. Bertram, G. Eisenbrand, Z. Krebsforsch., 85, 125 (1976).
2. P.P. Roller, D.R. Shimp, L.K. Keefer, Tetrahedron Lett., 2065 (1975).
3. P.N. Magee, E. Farber, Biochem J., 83, 114 (1962); A.E. Ross, L. Keefer, W. Lijinsky, J. Natl Cancer Inst., 47, 789 (1971).
4. W. Lijinsky, L. Keefer, J. Loo, A.E. Ross, Cancer Res., 33, 1634 (1973).
5. K. Eiter, K.F. Hebnbrock, H.J. Kabbe, Liebigs Ann. Chem., 765, 55 (1972).
6. M. Wiessler, Angew Chem., 86, 817 (1974); M. Wiessler Tetrahedron Lett., 2575 (1975).
7. J.E. Baldwin, S.E. Branz, R. Gomez, P.L. Kraft, A.J. Sinskey, S.R. Tannenbaum, Tetrahedron Lett., 333 (1976).
8. S.S. Hecht, C.B. Chen, D. Hoffman; 5th I.A.R.C. Meeting on Analysis and Formation of N-Nitrosamines, 1977, Durham, N.H.
9. H.L. Needles and K. Ivanetich, Chem. Ind. (London), 581 (1967).
10. O. Süs, S. Rosenberger, Ann, 564, 137 (1949).
11. Alkenes and esters might be formed after the free radical intermediate has undergone a one electron oxidation to a carbonium ion. For a review on the mechanism of oxidative decarboxylation see, J.K. Kochi, J. Am. Chem. Soc., 87, 1811 (1965); J. K. Kochi, ibid, 87, 3609 (1965); J.K. Kochi, J.D. Bacha, and T.W. Bethea III, ibid, 89, 6538 (1967).
12. W. Lijinsky, L. Keefer, J. Loo, Tetrahedron Lett., 26 5137 (1970).
13. Boiling Point of 3 was 98°C at 0.7 mm Hg.
14. R.R. Fraser, and Y.Y. Wigfield, Tetrahedron Lett., 2515 (1971); D. Seebach, D. Enders, Angew Chem., Internat. Edit, 11, 1101 (1972).