

## A NOVEL INTRAMOLECULAR REDOX REACTION: THE TRANSFORMATION OF L-PROLINE TO N-AMINO-2-PYRROLIDONES VIA A MESOIONIC SYSTEM

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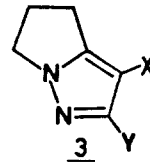
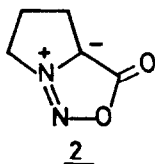
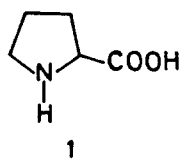
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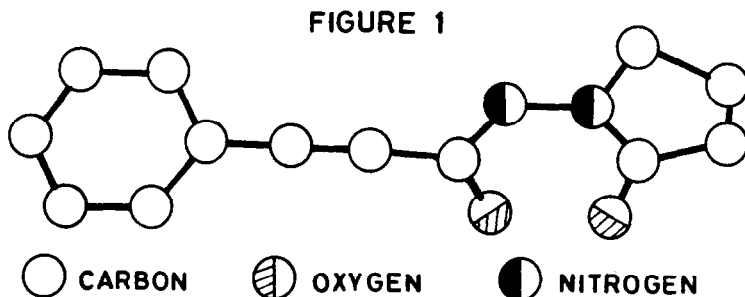
**Summary:** The mesoionic derivative of N-nitrosoproline (2), reacts with  $\text{PhC}\equiv\text{C}-\text{COOH}$  and TFA to form the N-amino-2-pyrrolidones 4 and 5 respectively. Compounds 4 and 5 are formed in good yield by a novel intramolecular redox process, and their structures were determined by x-ray diffraction.

During efforts to chemically simulate the microsomal  $\alpha$ -hydroxylation of N-nitroso amines<sup>1</sup>, the proline (1) derived mesoionic compound 2 was prepared.<sup>2</sup> Compound 2 reacted with a variety of acetylenes in a  $\pi 4_s + \pi 2_s$  fashion followed by the extrusion of  $\text{CO}_2$  to form 5,6-dihydro-4H-pyrrolo(1,2-b)-pyrazoles (3).<sup>2</sup> This transformation was used in a one step synthesis of the unusual natural product withasomnine (3; X=Ph, Y=H).<sup>3</sup> Unfortunately this synthesis

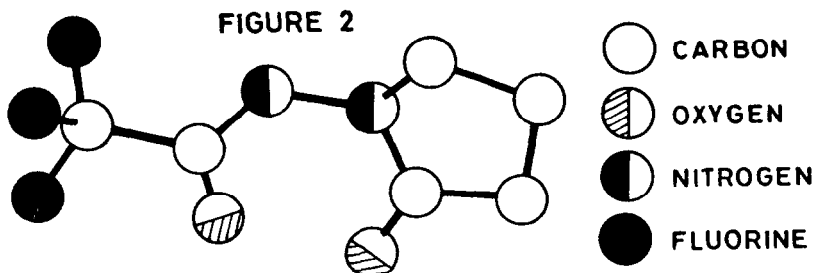


gave a mixture of withasomnine and the undesired regioisomer (3; X=H, Y=Ph) in the ratio of 1:3. Efforts to reverse the preference failed, and the cycloaddition of 2 with  $\text{PhC}\equiv\text{C}-\text{COOH}$  was investigated.<sup>4</sup> Careful analysis of the reaction mixture showed withasomnine (7%), its regioisomer (5%) and a major product (4, 86%) with unexpected physical properties.<sup>5</sup> The structure of 4 was elucidated by single crystal x-ray diffraction analysis. The crystals belonged to the orthorhombic space group  $P2_12_12_1$  with  $a=9.163(2)$ ,  $b=23.940(5)$ , and  $c=10.698(2)$  Å. All unique diffraction maxima with  $2\theta \leq 114^\circ$  were collected on a computer controlled four-circle diffractometer using graphite monochromated  $\text{Cu K}\alpha$  radiation (1.54178 Å) and variable speed,  $1^\circ$   $w$ -scans. Of the 1828 reflections measured, 1503 (82%) were judged observed after correction for Lorentz, polarization and background effects ( $F_o \geq 3\sigma(F_o)$ ).<sup>6</sup> The structure was solved routinely using direct methods and block

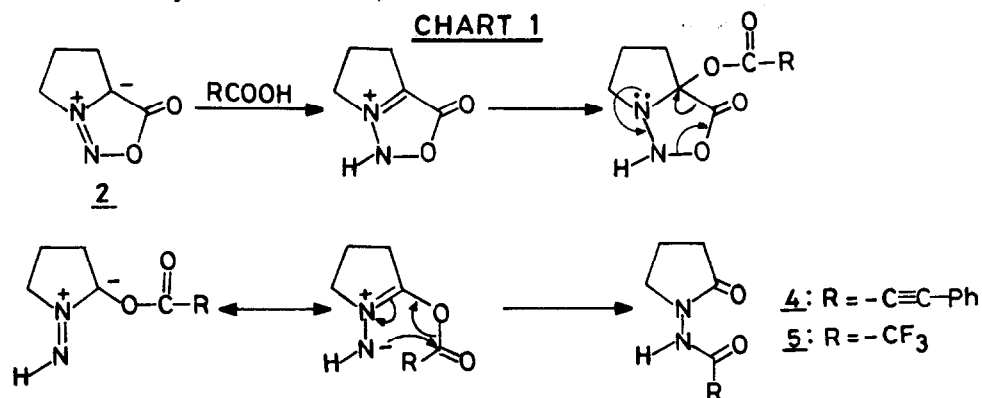
diagonal least squares refinements with anisotropic nonhydrogen atoms and isotropic hydrogens have converged to a conventional crystallographic residual of 0.057 for the observed reflections.<sup>7</sup> Figure 1 is a drawing of the final x-ray model of 4.



The structural assignment for 4 was also confirmed by comparison with an authentic sample prepared from the little studied<sup>8</sup> N-amino-2-pyrrolidone and  $\text{PhC}\equiv\text{C-COOH}$  in 63% yield.<sup>9</sup> The excellent yield (86%) of 4 from 2 and  $\text{PhC}\equiv\text{C-COOH}$  is particularly noteworthy since the overall change represents the oxidation of the  $\alpha$ -position of proline at the expense of the N-nitroso function. An apparently unrelated observation has led to the conclusion that the 2 to 4 transformation is a general one. The transformation of N-nitrosoproline to the mesoionic compound 2 is not easy, but could be brought about in nearly quantitative yields under well defined conditions with TFAA in dry ether followed by chromatography.<sup>2</sup> In early runs, the chromatography yielded in addition to 2, small amounts of colorless crystals, which, because of the closeness in m.p. were considered to be starting material. Subsequent observations revealed that this compound arose from the reaction of 2 with TFA<sup>10</sup> and that the novel compound can be obtained as the major product<sup>11</sup> under altered reaction conditions. The physical properties<sup>12</sup> of this substance were quite perplexing, especially the finding that it had incorporated the  $\text{CF}_3$  residue and that it rapidly liberated  $\text{CO}_2$  from aqueous bicarbonate. The structure of this material was also elucidated by x-ray diffraction and shown to be 5, and its formation can nicely be accounted for with a pathway precisely similar to that involved in the 2 to 4 change.



Crystals of **5** belonged to the monoclinic space group  $P2_1/c$  with  $a=9.675(1)$ ,  $b=9.891(2)$ ,  $c=9.253(2)$  Å, and  $\beta=112.04(3)^\circ$ . Data were collected and handled in the same manner as those for **4** and 912 reflections (83%) were judged observed. Block diagonal least squares refinements with anisotropic nonhydrogen atoms and isotropic hydrogens have converged to a standard crystallographic residual of 0.089 for the observed reflections.<sup>7</sup> A drawing of the final x-ray model is given in Figure 2. This x-ray result was also confirmed by the synthesis of **5** in 61% yield from N-amino-2-pyrrolidone and TFAA.<sup>13</sup> The electron withdrawing effect of the trifluoroacetyl group presumably is responsible for the acidity of **5** observed in the bicarbonate test. Compound **4** does not react with bicarbonate. The formation of **4** and **5** from **2** is rationalized by a mechanism put forward in Chart 1.<sup>14</sup>



The formation of **4** and **5** in good yields illustrates an unanticipated property of the bicyclic, strained mesoionic compound **2**. Apart from interest arising from the novel mechanistic pathway, we feel that the transformation is synthetically useful and has potential for further elaboration.

**Acknowledgements:** We are most grateful to Professor S. Ranganathan for helpful discussions, advice and encouragement. Financial assistance from DST, New Delhi is gratefully acknowledged. The Cornell workers thank NSF INT-8314133 for assistance.

## REFERENCES

1. This reaction is believed to be important in the transformation of N-nitroso compounds into carcinogenic substances. See Baldwin, J.E.; Branz, S.; Gomej, R.; Kraft, P.; Tannenbaum, S. *Tetrahedron Lett.* **1976**, 333.
2. Ranganathan, D.; Bamezai, S. *Tetrahedron Lett.* **1983**, 23, 1067.
3. Ranganathan, D.; Bamezai, S. *Synth. Comm.* **1985**, 15, 259.
4. A stirred solution of **2** (8 mmol) and  $\text{PhC}\equiv\text{CCOOH}$  (12 mmol) in dry xylene (20 ml) was refluxed for 50 hrs., the solvent was evaporated, and the residue was chromatographed on silica gel. Elution with benzene:EtOAc (4:1) gave **3** (X=H, Y=Ph) (5%) m.p. 89-90°C; with

benzene:EtOAc (7:3), withasomnine (3, X=Ph, Y=H) (7%) m.p. 118° C; and with EtOAc:MeOH (19:1), compound 4 (86%) m.p. 136-137° C. Upon recrystallization from EtOAc-hexane, 4 formed clear needles, m.p. 140-141° C. Elemental analysis was in agreement with expected values.

5. For 4: m.p. 140-141° C; IR (KBr)  $\text{cm}^{-1}$  3190(NH), 2220(strong, C≡C), 1690 (lactam), 1660, and 1530(amide); NMR ( $\text{CDCl}_3$ )  $\delta$  2.4 (m, 4H,  $-\text{CH}_2-\text{CH}_2-$ ), 3.8 (t, 2H,  $-\text{CH}_2-\text{N}-$ ), 7.4 (m, 5H, Ph), 9.5 (s, 1H, NH,  $\text{D}_2\text{O}$  exch.); MS  $m/z$  228( $\text{M}^+$ ), 129 ( $\text{Ph}-\text{C}\equiv\text{CCO}^+$ ).

6. All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 78, MULTAN 80, and RANTAN 80, systems of computer programs for the automatic solution of crystal structures from x-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson, University of York, England, 1978 and 1980; BLS78A, an anisotropic block diagonal least squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University, 1978.

7. Crystallographic parameters have been deposited with the Cambridge Crystallographic Data File, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, ENGLAND and are available from them. Please give a complete literature citation when ordering.

8. Michels, J.J.; Gever, W.G. *J. Am. Chem. Soc.* 1956, 78, 5349 and Zubeck, H. *Z. Chem.* 1969, 9, 58. We have found the latter, reductive procedure to be superior.

9. A solution of N-amino-2-pyrrolidone (3 mmol),  $\text{PhC}\equiv\text{CCOOH}$  (2 mmol) and DCC (3 mmol) in dry dioxane (50 ml) was stirred at room temperature for 3 days, the DC urea filtered off, and the filtrate evaporated in vacuo. Preparative tlc using EtOAc as developer gave 63% of 4, m.p. 140-141° C.

10. The reaction of N-nitrosoprolinone with TFAA in dry ether for 6 hrs. followed by evaporation and chromatography of the residue without delay gives 2 (96%) and no 5 by tlc. However, when the residue is kept in the refrigerator for ~2 days and then chromatographed, 5 is isolated in ~15% yield. Presumably 5 is formed by reaction of 2 with TFA.

11. Compound 5 can be isolated in 50% yields by continuing the reaction of 2 with TFAA in ether until the conversion to 5 is complete by tlc, evaporation of solvents, chromatography on silica gel with benzene:EtOAc (3:7) elution.

12. For 5: m.p. 110° C; IR (KBr)  $\text{cm}^{-1}$  3250, 3190(NH), 1745(lactam), 1685, and 1525(amide); NMR ( $\text{CDCl}_3$ )  $\delta$  2.34 (m, 4H,  $-\text{CH}_2-\text{CH}_2-$ ), 3.68 (t, 2H,  $-\text{CH}_2-\text{N}-$ ), 10.4 (s, 1H, NH,  $\text{D}_2\text{O}$  exch.); MS  $m/z$  196( $\text{M}^+$ ), 99 ( $\text{M}^+ - \text{COCF}_3$ ).

13. A solution of N-amino-2-pyrrolidone (1 mmol) and TFAA (1 ml) in dry benzene (10 ml) was left stirred for 6 hrs, evaporated, admixed with water, extracted with benzene, dried ( $\text{MgSO}_4$ ), and evaporated in vacuo. The residue was recrystallized from benzene-hexane to give 61% of 5, m.p. 110° C.

14. We are grateful to a referee for suggestions about the mechanism.

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