Tetrahedron Letters,Vol.24,No.10,pp 1067-1070,1983
Printed in Great Britain

0040-4039/83/101067-04$03.00/0

A NOVEL PROLINE DERIVED MESO-IONIC SYNTHON

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ABSTRACT: A practical route to the strained 5,6-dihydro-4H-pyrrolo[1,2-b]-pyrazoles has been accomplished by "pyrazole annulation" on the proline ring, via the novel and strained meso-ionic, 5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]oxadiazolone (3).

The recent demonstration of the mutagenic nature of α-acetoxynitrosopyrrolidine (αPN), without microsomal activation, supports the idea that the metamorphosis of N-nitroso amines to carcinogens takes place by way of microsomal hydroxylation[1]. During endeavours chemically to simulate such a biological α-hydroxylation, from the N-nitroso derivative of the amino acid L-proline (1) as the starting material, a novel meso-ionic system was encountered, which is the focus of the present communication.

Treatment of N-nitrosoproline[2,3] (2) with trifluoroacetic anhydride (TFAA) leads to the meso-ionic system 3 in 96% yields. In a typical procedure, a solution of 2 in dry ether (10 mmol, 100 ml) was admixed with TFAA (10 mmol), left stirred for 6 hr at 0°C, evaporated, chromatographed on a short column of silica gel and eluted with benzene: EtOAc (7:3) to yield 3 as a pale yellow oil, bp 140°/0.02 torr (CHART I). The structural assignment for 3 is supported by analytical[5] and spectral[6] data. In spite of the fact that it is a strained meso-ionic system, compound 3 is quite stable. It was recovered completely unchanged after refluxing in dry methanol for 4 hr, thus excluding the possibility of its involvement in the reported ready esterification of N-nitrosoproline on attempted crystallization from alcohols[4].

In agreement with the expected properties of 3, it underwent, with an array of acetylenes, smooth $\pi 4_s + \pi 2_s$ additions, followed by extrusion of CO_2 on refluxing in xylene, leading to the substituted 5,6-dihydro-4H-pyrrolo[1,2-b]-pyrazoles, 4a-4e[6,7,8] (CHART II). The details related to the preparation of 4a-4e are presented in TABLE I.

The high reactivity of the meso-ionic system 3 is further reflected in its reaction with acenaphthylene leading to the un-anticipated $\pi 4_s + \pi 2_s$ product 5[6] and the CO_2-extruded 6[6], and with acrylonitrile to the regio-isomers 7 and 8[9] arising from cyclo-addition and loss of CO_2[10] (CHART III).

The ready formation of the meso-ionic unit within the bicyclo[3.3.0]octane framework is of interest and compound 3 should prove to be a useful synthon for

CHART I

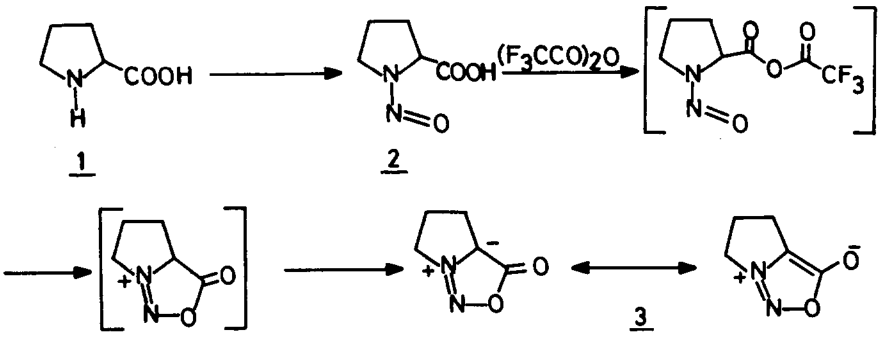
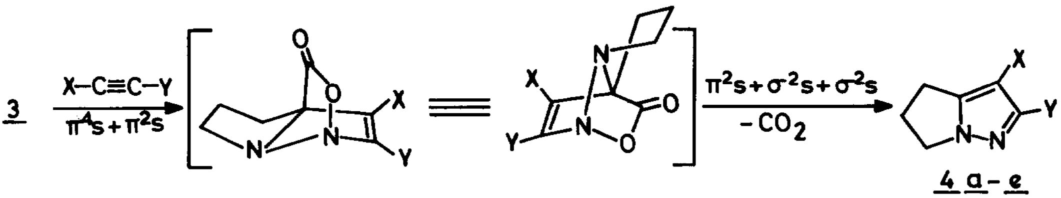
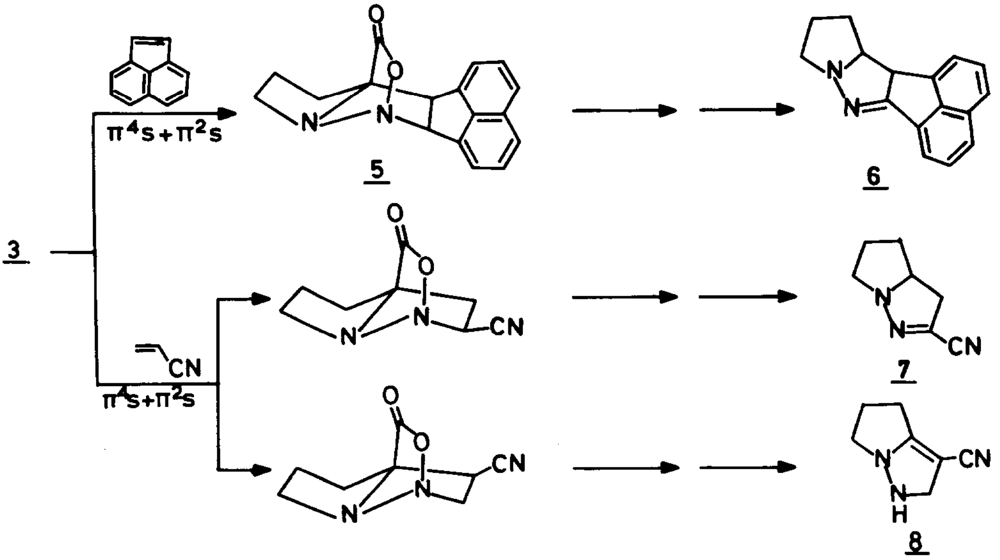


CHART II



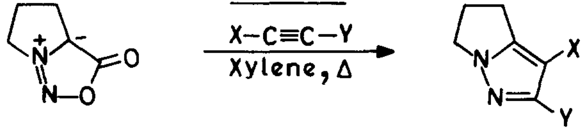
a: X = Y = Ph ; b: X = Y = CO_2Me ; c: X = H , Y = CO_2Et ;
d: X = CO_2Et , Y = H ; e: X = Y = COPh

CHART III



systems such as 4 and others[11]. Further reactions of 3 and that of the even more strained meso-ionic system derivable from the naturally occurring L-azetidine 2-carboxylic acid are under investigation.

TABLE I[a]



3 (1 mmol) 4

$X-C\equiv C-Y$	mmol	time (hr)	Product	Yield (%)	mp (°C)
PhCO-C≡C-COPh	1.2	8	4e	92	137
$MeO_2C-C\equiv C-CO_2Me$	3.0	8	4b	80	73
Ph-C≡C-Ph	1.2	48	4a	45	160
$H-C\equiv C-CO_2Et$	3.0	8	4c[9]	40	-
			4d	35	-

a. The reactions were monitored by tlc. Solvents were evaporated and the pure product(s) isolated by chromatography on silica gel and elution with benzene: ethyl acetate.

Acknowledgements: We are very grateful to Professor S. Ranganathan for valuable discussions and to the referee for most useful and constructive suggestions. Financial assistance from U.G.C., New Delhi is gratefully acknowledged.

References:

1. J. E. Baldwin, S. Branz, R. Gomej, P. Kraft, A. Sinskey and S. Tannebaum, Tetrahedron Lett., 333 (1976).
2. W. Lijinsky, L. Keffer and J. Loo, Tetrahedron, 5137 (1970).
3. N-Nitrosoproline was prepared essentially according to the procedure described in the above paper. The product was more conveniently isolated by extraction with CH_2Cl_2 from the aqueous acidic medium and crystallized from benzene; yield 84%; mp 106-107°C (lit^2 100-101°C); $[\alpha]_D^{25} = -189°$ (C=6.0, H_2O) (Lit^2 $[\alpha]_D^{25} = -185°$ (C=0.23, H_2O) ir: ν(max) (KBr) cm^{-1}: 1450, 1730; nmr: $\delta(CDCl_3)$: 2.2 (m, 4H, $-CH_2-CH_2-$), 3.7 (t, 1H, HC-N), 4.4 (t, 2H, H_2C-N); m/e: 144 (M^+), 99 (M^+-COOH), 69 ($M^+-(NO+COOH)$).
4. ".....earlier preparations in which the nitrosoproline was crystallized from methanol or from technical acetone (containing isopropanol) led to conversion of the nitrosoproline into the methyl and isopropyl esters respectively...." (ref 2, p 5151). The activating effect of the nitroso group on a proximate electron acceptor has been established (S. K. Chang, G. W. Harrington, H. S. Veele and D. Swern, J. Org. Chem., 41, 3752 (1976).
5. Satisfactory analytical values have been obtained for all compounds.
6. 3: ir: ν(max) (neat) cm^{-1}: 1770, 1730; nmr: $\delta(CDCl_3)$ 2.57 (m, 4H, $-CH_2-CH_2-$), 4.37 (t, 2H, H_2C-N); m/e: 126 (M^+), 96 (M^+-NO), 68 ($M^+-(NO+CO)$). 4a: ir: ν(max) (KBr) cm^{-1} 1600; nmr; $\delta(CDCl_3)$ 2.58 (m, 2H, H_2C-), 2.85 (m, 2H, H_2C-Ar), 4.12 (t, 2H, H_2C-N); m/e: 260 (M^+). 4b: ir: ν(max) (KBr) cm^{-1} 1720; nmr: δ ($CDCl_3$) 2.6 (m, 2H, H_2C-), 3.0 (m, 2H, H_2C-Ar), 3.7, 3.83 (s, s, 3H, 3H, H_3COOC-), 4.08 (t, 2H, H_2C-N); m/e: 224 (M^+). 4c: ir; ν(max) (neat) cm^{-1} 1700; nmr: δ ($CDCl_3$) 1.3 (t, 3H, H_2C-CH_3), 2.65 (m, 2H, H_2C-), 3.0 (m, 2H, H_2C-Ar), 4.2

(m, 4H, H_2C-N, -OCH_2CH_3), 7.65 (s, 1H); m/e: 180 (M^+), 107 (M^+-CO_2Et). 4d: ir: ν(max) (neat) cm^{-1} 1730; nmr: δ($CDCl_3$) 1.35 (t, 3H, H_2C-CH_3), 2.7 (m, 4H, H_2C-H_2C-Ar), 4.2 (m, 4H, H_2C-N, -OCH_2CH_3) 6.35 (s, 1H); m/e: 180 (M^+), 107 (M^+-CO_2Et). 4e: ir: ν(max) (KBr) cm^{-1} 1650, 1630; nmr: δ($CDCl_3$) 2.55 (m, 2H, H_2C-), 2.85 (m, 2H, H_2C-Ar), 4.12 (t, 2H, H_2C-N); m/e: 316 (M^+), 239 (M^+-Ph), 211 (M^+-PhCO). 5: syrup; yield 22%; ir: ν(max) (neat) cm^{-1} 1745; nmr: δ ($CDCl_3$) 2.85 (d, d, 2H, HC), 4.2 (t, 2H, H_2C-N); m/e: 278 (M^+); 234 (M^+-CO_2). 6: mp 173-174°; yield 26%; ir: ν(max) (KBr) cm^{-1} 1630; m/e: 233 (M^+-H). 7: mp 155-157°; yield 41%; ir: ν(max) (KBr) cm^{-1} 2240; nmr: δ($CDCl_3$) 3.6 (m, 1H, HC-N), 4.2 (t, 2H, H_2C-N); m/e: 135 (M^+), 108 (M^+-HCN). 8: mp 134-136°; yield 14%; ir: ν(max) (KBr) cm^{-1} 3300, 2245; nmr: δ($CDCl_3$) 3.3 (m, 4H, H_2C-N, H_2C-NH), 4.2 (br, 1H, HN); m/e: 135 (M^+), 109 (M^+-CN).

7. The meso-ionic compound prepared from proline by successive thiobenzoylation and cyclization with Ac_2O or TFA undergoes cyclo-addition reactions with loss of COS (G. C. Barrett and R. Walker, *Tetrahedron*, 32, 579 (1976)).

8. A variety of substituted pyrazoles can be prepared *via* cyclo-addition to sydnones (R. Huisgen and H. Gotthardt, *Chem. Ber.*, 101, 1059 (1968) and references cited therein.

9. The regioselectivity in cyclo-additions involving sydnones - a substituted azomethine imine system - has been elegantly rationalized from data related to frontier orbital energies and coefficients generated from experimental values for ionization potentials, electron affinity and M.O. (HMO, ω-HMO, PPP, CNDO/2, INDO, EH) calculations. The cyclo-additions are largely LU controlled. However in sydnones, unlike the parent azomethine imine, the terminal coefficients are quite close, thus leading to a decrease in regioselectivity in all cyclo-additions. This trend is accentuated with acetylenic dipolarophiles because of slightly more HO control. The results from the present work involving olefinic and acetylenic dipolarophiles are in good agreement with these conclusions (K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier and J. K. George, *J. Amer. Chem. Soc.*, 95, 7287 (1973); K. N. Houk, J. Sims, C. R. Watts and L. J. Luskus, *ibid.*, 95, 7301 (1973)).

10. The cyclo-addition with acrylonitrile was carried out with the objective of the generation of the parent system 4 (X=Y=H). This expectation was based on the reported formation of N-phenyl pyrazole in 78% yields by cyclo-addition of 3-phenylsydnone with acrylonitrile involving loss of CO2 and HCN (V. F. Vasileva, V. G. Yashunskii and M. N. Shchukina, *Chem. Abstr.*, 54, 24674 (1960); 55, 22291 (1961); 60, 8017 (1964)).

11. Interestingly, structure 4 (X=Ph, Y=H) has been assigned to the alkaloid Withasomnine on the basis of physical properties (H.-B. Schroter, D. Neumann, A. R. Katritzky and F. J. Swinbourne, *Tetrahedron*, 22, 2895 (1966). We are grateful to the referee for bringing this paper to our notice.

(Received in UK 4 January 1983)