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# SELECTIVE REDUCTION AND CLEAVAGE OF THE N-N BOND OF FUSED TETRAHYDROPYRIDAZINES: A ROUTE TO FUNCTIONALISED LACTAMS

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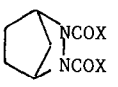
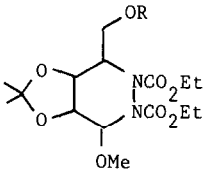
Summary: The C=N bond of 4,4a,5,6-tetrahydropyrrolo[1,2-b]pyridazin-7(3H)-ones (3) is reduced with high stereoselectivity by hydrogen over Adams' catalyst; the products (6) are N-acetylated and the N-N bond can then be cleaved by sodium in liquid ammonia to give the lactams (7).

The reductive cleavage of the N-O bond of cyclic oximes and hydroxylamines is a key step in many recent target syntheses.[1] Reductive cleavage of an N-N bond is more difficult and has consequently been used much less often. A systematic investigation of methods of reductive cleavage of bridged hexahydropyridazines (1) (X = OEt, $CF_3$) has been reported by Mellor and Smith.[2] Schmidt and his co-workers have used this type of reductive cleavage on pyridazines such as (2) as a route to aminosugars.[3] The cleavage of the N-N bond of a fused tetrahydropyrazole was an important step in a recent synthesis of saxitoxin.[4]



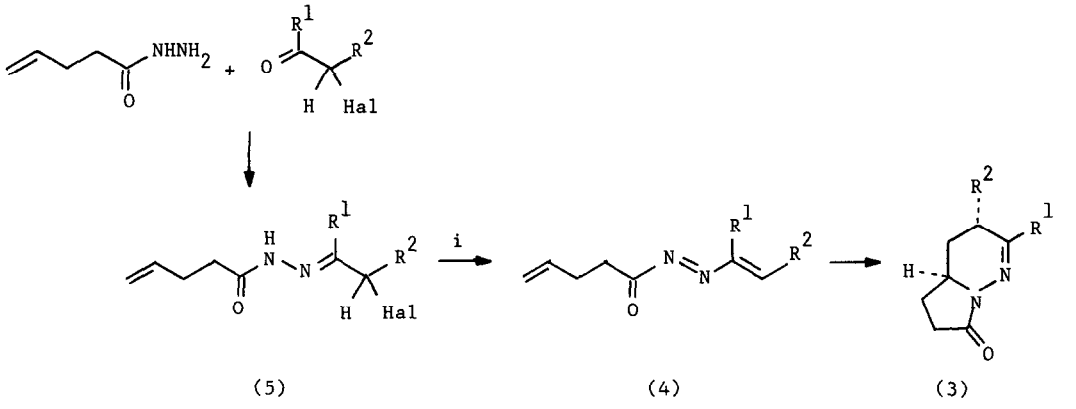

(1)




(2)

We have described a synthesis of 4,4a,5,6-tetrahydropyridazin-7(3H)-ones (3) involving intramolecular cycloaddition of azoalkenes (4). These azoalkenes are formed as transient intermediates by dehydrohalogenation of hydrazones (5) derived from pent-4-enoic acid hydrazide and halocarbonyl compounds (Scheme 1).[5] We have extended the reaction sequence to several other hydrazones including those formed with 1,3-dichloroacetone [compound (5a)] and with 3-chlorobutan-2-one [compound (5e)].# The cycloadducts (3) can be isolated in good yield from a reaction procedure in which the hydrazones (5) are formed in situ and then treated with sodium carbonate under high dilution.[6] With azoalkenes

(4e) and (4f) the cycloaddition is highly diastereoselective: isomers (3e) and (3f), respectively, are the only products detected. This can be ascribed to a preferred anti-trans[7] transition state for the intramolecular addition.



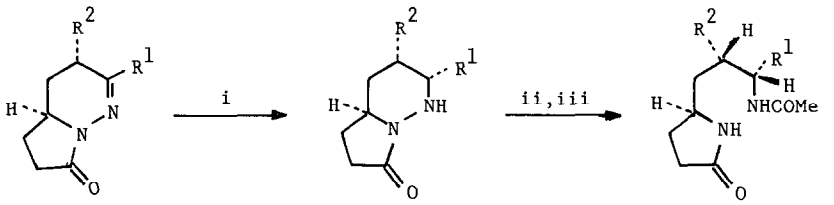

(3), (4), (5) a; $R^1 = CH_2Cl$, $R^2 = H$
b; $R^1 = Ph$, $R^2 = H$
c; $R^1 = CO_2Et$, $R^2 = H$
d; $R^1 = Me$, $R^2 = H$
e; $R^1 = R^2 = Me$
f; $R^1R^2 = (CH_2)_4$
(3) g; $R^1 = CH_2OEt$, $R^2 = H$
h; $R^1 = CO_2H$, $R^2 = H$

SCHEME 1. Reagent: i, $Na_2CO_3$.

The ether (3g) was prepared from the chloromethyl compound (3a) by reaction with ethanolic potassium hydroxide, and the acid (3h) was obtained by hydrolysis of the ester (3c). Compounds (3) (c—h) were cleanly reduced to the hexahydropyridazinones (6) by the action of hydrogen over Adams' catalyst.[8] Within the limits of detection by t.l.c. and by $^1H$ n.m.r. these reductions were completely stereoselective, attack taking place on the face opposite to that bearing the axial bridgehead hydrogen (4a-H). In contrast, reduction by aluminium amalgam was not stereoselective and, in the case of compound (3b), led to the formation of a mixture of (6b) and its diastereomer with inverted configuration at C-2. The structures of the reduction products (6) were deduced from the $^1H$ n.m.r. spectra. In the spectra of compounds (6b), (6c), and (6d) the signals for 2-H all showed a large vicinal coupling constant, indicating a trans-diaxial relationship between 2-H and one of the hydrogens attached to 3-H. On the other hand the 2-H to 3-H coupling constant in compound (6e) was small, and was consistent with an axial—equatorial relationship of the two hydrogens.[9]

There was no evidence for reductive cleavage of the N-N bond in any of these reactions. This is in contrast to reactions of analogous 4H-1,2-oxazines, in which the N-O bond is reductively cleaved by these reagents.[10] The N-N bonds of compounds (6d), (6e), (6f), and (6g) were, however, successfully cleaved by the method outlined in Scheme

2. N-Acetylation followed by reaction with sodium in liquid ammonia gave the corresponding pyrrolidones (7) in good overall yield.[11] As with the earlier examples of N-N bond cleavage[2,3,4] it proved necessary for both nitrogen atoms to be activated by acylation in order to achieve efficient cleavage of the bond.




(3) (6) (7)

[$R^1$ and $R^2$ in (6) and (7) as in (3)]

SCHEME 2. Reagents: i, $H_2$, $PtO_2$, HCl; ii, MeCOCl or $(MeCO)_2O$; iii, Na, $NH_3$.

The overall sequence of reactions provides a simple and highly selective route to functionalised pyrrolidones and thence to diamines. We have found that the intramolecular cycloaddition reactions can be extended to hydrazides of several other terminally unsaturated acids including hex-5-enoic acid, cyclopent-2-eneacetic acid, and allyloxyacetic acid. The reductive cleavage is therefore potentially a much more general synthetic route to functionalised lactams.

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# Satisfactory analytical and spectroscopic data were obtained for new compounds.

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6 Typical experimental procedure [for compound (3f)]: A solution containing 2-chlorocyclohexanone (1.59 g, 12 mmol) and pent-4-enoic hydrazide[5] (1.37 g, 12 mmol) in ether (50 mL) was stirred at 20°C for 2 h. It was then added dropwise to a vigorously stirred suspension of sodium carbonate (10.0 g) in dichloromethane (600 mL) and the mixture was stirred for 48 h. It was filtered through Celite and the filtrate was evaporated to dryness. Flash chromatography gave the pyrrolopyridazinone (3f) (1.79 g, 78%), m.p. 117—118°C (from ethyl acetate—hexane) (lit.,[5] 33%; m.p. 114—115°C).

7 E. Ciganek, Org. React., **32**, 1 (1984).

8 Typical experimental procedure [for compound (6f)]: A solution containing compound (3f) (4.60 g, 24 mmol) and HCl (5 drops) in ethanol (150 mL) was stirred under hydrogen at atmospheric pressure with platinum(IV) oxide (300 mg) for 30 h. After removal of the catalyst the product was subjected to flash chromatography which gave the pyridazinone (6f) (4.19 g, 90%), m.p. 59—61°C (from ethyl acetate).

9 N.m.r. data (for 2-H): (6b): δ 3.70 (dd); $J_{23}$ 11.0 and 2.0 Hz; (6c): δ 3.46 (dd, partly overlapping with signal for 4a-H); $J_{23}$ (ax-ax) 11.0 Jz; (6d): δ 2.82 (ddq); decoupling gives $J_{23}$ 10.3 and 2.5 Hz; (6e): δ 3.01 (dq); $J_{23}$ 2.7 Hz.

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11 Typical experimental procedure [for compound (7f)]: The pyridazinone (6f) (1.20 g, 6.0 mmol) was acetylated by heating in acetic anhydride (25 mL) under reflux for 30 min. This gave the N-acetyl derivative (1.36 g, 95%), m.p. 110°C. This derivative (1.20 g) was dissolved in a mixture of THF (10 mL) and dry liquid ammonia (30 mL) and to the solution, maintained under reflux, was added sodium (0.25 g) during 1.5 h. The reaction mixture was quenched with ammonium chloride and the pyrrolidinone (7f) (1.01 g, 83%), m.p. 204°C, was extracted with dichloromethane.

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