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Rhodium-Catalysed Hydroformylation and Carbonylation of *N*-Alkenyl-1,3-diaminopropanes[1]

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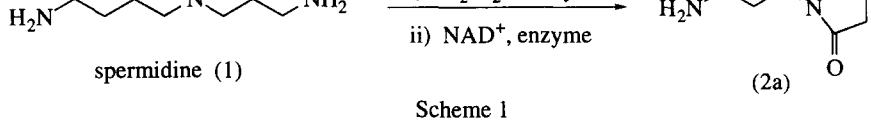
Abstract: The rhodium catalysed reactions of *N*-alkenyl-1,3-diaminopropanes with H_2/CO usually give mixtures of diazabicycloalkanes and aminopropyl lactams. The chemo- and regioselectivity of these reactions are influenced by the choice of ligand and by the ratio of H_2 and CO in the gas mixture and in some cases formation of a single compound can be achieved. © 1997 Elsevier Science Ltd.

INTRODUCTION

Rhodium-catalysed reactions of unsaturated amines with H_2/CO mixtures are the subject of current investigation as potential routes to heterocyclic compounds. In general it has been shown that reactions of unsaturated anilines and alkenamides give products arising from initial hydroformylation reactions.[2,3,4,5,6] In contrast it has long been established that reactions of unsaturated aliphatic amines can give products arising from carbonylation reactions.[6,7,8,9] In many cases mixtures of products arising from hydroformylation and carbonylation are obtained.[9,10,11]

Aliphatic polyamines such as spermine and spermidine (1) are widely distributed in nature and their oxidation products have been the subject of physiological and pharmacological interest.[12] (Scheme 1).



spermidine (1) (2a)

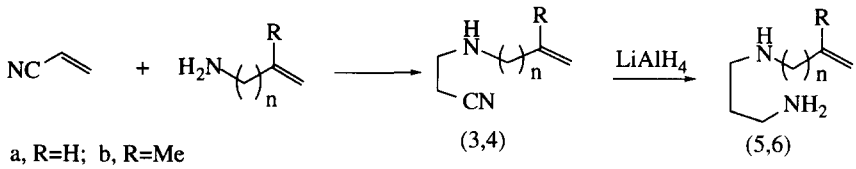
Scheme 1

In this paper we describe attempts to establish a general route to these classes of compounds based on rhodium-catalysed reactions of *N*-alkenyl-1,3-diaminopropanes with H_2/CO.

RESULTS AND DISCUSSION

Preparation and reactions of N-alkenyl-1,3-diaminopropanes

The diamines were prepared by lithium aluminium hydride reduction[13] of the corresponding 3-alkenylamino propanenitriles which in turn were obtained by addition of the unsaturated amine to acrylonitrile.[14] (Scheme 2). The yields of the nitriles and the corresponding amines are summarised in Table 1.



a, R=H; b, R=Me (3,4) (5,6)

Scheme 2

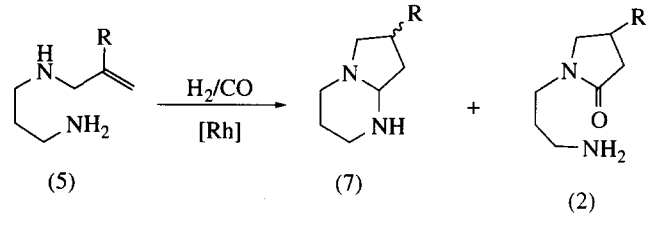
Table 1 Yields of *N*-(alkenylamino)propanenitriles (3,4) and 1,3-diaminopropanes (5,6)

R	n	Propanenitrile	Yield %	Diaminopropane	Yield %
H	1	(3a)	92	(5a)	70
Me	1	(3b)	100	(5b)	80
H	2	(4a)	73	(6a)	95
Me	2	(4b)	42	(6b)	40

The amines (5,6) were initially reacted in benzene at 80 or 100°C with H_2/CO, 1:1 (2.7 MPa, 400 p.s.i.) in the presence of $[Rh(OAc)_2]_2$ and triphenylphosphine in the molar ratio of 200:1:4 such that vacant sites were available on the metal for potential coordination to the amino nitrogen atoms. The product ratios were estimated from the ^{13}C n.m.r. spectra of the total product mixture.

Reactions of N-allyl-1,3-diaminopropane (5a)

Reaction of the allylamine (5a) under the standard conditions at 80°C (see above) gave a mixture of 1,5-diazabicyclononane (7a) and the 2-pyrrolidinone (2a) (Scheme 3) in a ratio of *ca.* 40(7a) to 60(2a). The formation of products arising both from initial hydroformylation (7a) and carbonylation (2a) reactions is in



(5) (7) (2)

a, R=H; b, R=Me Scheme 3

agreement with the reported rhodium-catalysed reactions of allylamine[10] and *N*-benzylpent-4-enylamine.[9] It has been demonstrated that these products arise from intramolecular competition between hydrogen and the amine nitrogen in cleavage of the intermediate acylrhodium complex.[9,10,11] The product ratio was kinetically controlled in that the lactam (2a) did not cyclise via an aminal to (7a) when put back under the reaction conditions. The unreactivity of related lactams has been demonstrated previously.[2,6] The exclusive formation of products (2a, 7a) resulting from terminal C–C–bond formation has been shown previously.[2,3,7,8,10] and proposed to be due to chelation of the nitrogen leading to a 5-rather than a 4-membered cyclic σ-alkyl intermediate. The diazabicyclononane (7a) was distilled from the product mixture, the residue acetylated and the aminopropyl pyrrolidinone (2a) isolated as its *N*-acetyl derivative. A reaction of (5a) carried out under similar conditions but in ethyl acetate gave a mixture of (7a) and the *N*-acetyl derivative of (2a) in a ratio of *ca.* 30:70.

The effect of varying gas composition on the chemoselectivity of the reaction of (5a) is summarised in Table 2. The ratio of products could be dramatically changed by varying the H_2/CO ratio from 9:1 to 1:9. A similar shift to the formation of carbonylation products on using CO-rich gas mixtures has been previously described.[9]

Table 2. Effect of gas composition on chemoselectivity for reactions of the amine (5a)

Ratio H_2/CO	Product distribution	
	Hydroformylation (7a)	Carbonylation (2a)
9 : 1	95	5
1 : 1	40	60
1 : 9	10	90

The effect of varying the ligand on the chemoselectivity of reaction was also investigated (Table 3). No clear cut correlation with either the electronic parameters (basicity) or steric parameters of Tolman[15] were observed. However in general hydroformylation was more favoured by the more basic ligands, e.g. P(*n*-Bu)$_3$ and P(Cy)$_3$ and carbonylation by more bulky ligands especially P(*o*-Tol)$_3$.

Table 3. Effect of ligand variation on chemoselectivity for reactions of the amine (5a)

Ligand PR_3 R	Electronic parameter[15] (basicity) ν (cm^{-1})	Steric parameter[15] θ (degrees)	Product distribution Hydroformylation (7a) : Carbonylation (2a)
OPh	2085.3	128	50 : 50
O-*o*-Tol	2084.1	141	25 : 75
O-Cy	~2076[a]	~130[a]	80 : 20
Ph	2068.9	145	40 : 60
o-Tol	2066.4	194	15 : 85
n-Bu	2060.3	132	95 : 5
Cy	2056.1	170	85 : 15

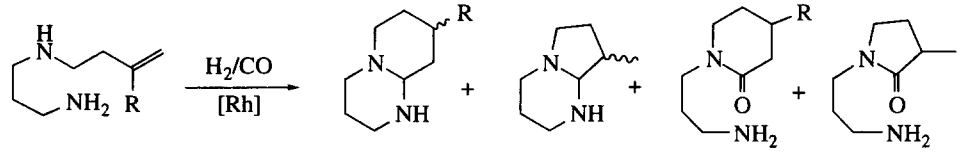
[a]Values for tri*iso*propyl phosphite[15]

Attempts to achieve even higher chemoselectivity involved the choice of an appropriate combination of ligand and gas ratio. Thus use of a 9:1 H_2/CO gas ratio with P(Cy)$_3$ gave only the diazabicyclononane (7a) together with small amounts (< 10%) of non-lactam containing material. Attempts to direct the chemoselectivity to carbonylation were also made. However, a reaction using a 1:9 H_2/CO ratio together with P(*o*-Tol)$_3$ still gave *ca.* 15% of the hydroformylation product (7a) thus showing no improvement over the ratios shown in Tables 2 and 3.

Several reports have appeared recently of the use of the hindered bisphosphite, BIPHEPHOS[16,17,18,19] which shows strong regioselective preference for the formation of terminal aldehydes from 1-alkenes. Although regioselectivity is not a problem in reactions of (5a) (see above) use of this ligand was studied and found perhaps surprisingly to give complete chemospecificity with the hydroformylation product (7a) being formed as the sole product in quantitative yield.

Reactions of N-(but-3-enyl)-1,3-diaminopropane (6a)

Reactions of the *N*-butenyl compound (6a) gave mixtures of regioisomers resulting from both hydroformylation and carbonylation (Scheme 4).



(6) (8) 9 (10) (11)

a, R=H; b, R=Me

Scheme 4

The effects of varying the ligand on the chemo- and regio-selectivity of the reaction are summarised in Table 4.

The effect of ligand on the chemoselectivity of reaction was similar to that observed in reactions of the *N*-allyl compound (5a) in that the highly basic alkylphosphines gave predominantly hydroformylation products (8a and 9) and the very bulky P(*o*-Tol)$_3$ gave predominantly carbonylation products (10a and 11).

The regioselectivity of hydroformylation agreed with that reported previously[20,21] in that a high preference for products arising from terminal aldehydes was observed when less basic aryl phosphines were used. In addition, it has been noted previously that use of the bulky but basic P(Cy)$_3$ in place of PPh$_3$ led to an increase of branched-chain products in agreement with the results in Table 4. These results suggest that there is little influence of the nitrogen atoms on the regioselectivity of the hydroformylation of the butenylamine (6a) in contrast to their proposed influence on the regioselectivity of the allyl homologue (5a). Possibly, nitrogen complexation is equally facile in the transition states leading to either terminal or internal hydroformylation.[9] Addition of a large excess of PPh$_3$ to a reaction led to no change in selectivity (Table 4). These results thus contrast with reaction of a related butenyl phosphine where chelation control was proposed to explain regiospecific internal hydroformylation.[22]

Changes in the added ligands led to very little variation in the regiochemistry of the carbonylation reaction (Table 4). Interestingly, regioselectivity of carbonylation was opposite to that of the hydroformylation reaction in that 5-membered ring products arising from C-C bond formation at the internal carbon were obtained. This suggests that when the nitrogen atom is involved in the transition state, i.e. in carbonylation reactions, chelation control must become important and preferential reaction at the internal carbon mirrors that reported for the related phosphines.[22] In addition, amine directed chelation control of carbonylation was also observed by Ojima.[9]

The effect of changing the gas composition on both the reaction chemoselectivity and the product regioselectivity was studied using triphenylphosphine and BIPHEPHOS as ligands. The results in Table 4 for reactions using triphenylphosphine show similar trends in chemoselectivity to those showed by the allylamine (5a) (Table 2). The regioselectivity of the hydroformylation product shows changes with gas ratio. The higher the partial hydrogen pressure the less the percentage of linear aldehyde derived product. This contrasts with the results quoted for hydroformylation of hex-1-ene using a similar rhodium catalyst system where increases in partial hydrogen pressure led to an increase in the proportion of linear aldehyde.[20,23] The reason

Table 4. Effect of gas composition and ligand variation on chemoselectivity and regioselectivity of reactions of the N-butenylamine (6a)†

Ligand	Ratio H_2/CO	Product ratio	Ratio of regioisomers	
		Hydroformylation (8a,9) : Carbonylation (10a,11)	Hydroformylation linear (8a) : branched (9)	Carbonylation linear (10a) : branched (11)
BIPHEPHOS	9 : 1	100 : 0	>95 : < 5	-
	1 : 1	100 : 0	100 : 0	-
	1 : 9	100 : 0	100 : 0	-
$P(OPh)_3$	1 : 1	75 : 25	85 : 15	25 : 75
PPh_3	9 : 1	> 95 : < 5	70 : 30	-
	1 : 1[a]	60 : 40	85 : 15	25 : 75
	1 : 1[b]	60 : 40	85 : 15	25 : 75
	1 : 9	20 : 80	> 95 : < 5	55 : 45
P(*o*-Tol)$_3$	1 : 1	5 : 95	95 : 5	30 : 70
P(*n*-Bu)$_3$	1 : 1	>95 : < 5	75 : 25	-
$P(Cy)_3$	1 : 1	> 95 : < 5	65 : 35	-

†Most reactions were repeated two or three times with little variation in product ratio; average values are given.
[a]Initial pressure 400 or 1200 psi H_2/CO
[b]20 equivalents PPh_3 per $[Rh(OAc)_2]_2$

for the differences between the two systems is not known but the results suggest that although there is no evidence that the N atoms are involved in intramolecular chelation to an alkene-rhodium complex, they may be involved in intermolecular coordination with rhodium leading to a significantly different transition state to that involved in the reaction of hex-1-ene.

Reactions of the butenylamine (6a) using BIPHEPHOS as ligand gave (8a) as the almost exclusive product over a range of gas mixtures from 9:1 to 1:9 H_2/CO; only with a high partial H_2 pressure was a trace of (9), the product derived from internal hydroformylation obtained. No products arising from carbonylation were detected.

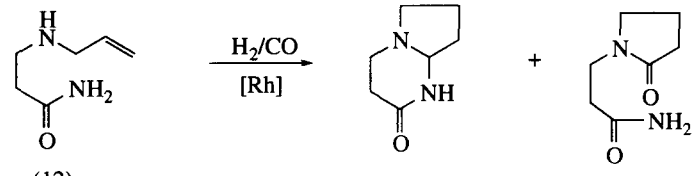
Reactions of N-(methylallyl)-1,3-diaminopropane (5b) and N-(3-methylbut-3-enyl)-1,3-diaminopropane (6b)

Reactions of the methyl-substituted alkenes (5b) and (6b) using PPh_3 as ligand were slower than those of the alkenes (5a) and (6a) above and gave a predominance of the carbonylation product over the hydroformylation product (Schemes 3 and 4). The slower reaction and the regioselectivity were due to the increased steric demand in the transition state imposed by the additional methyl group and this could also be responsible for the predominance of carbonylation versus hydroformylation in keeping with the trends discussed above. Reaction of (5b) gave some starting material (*ca.* 10%) together with a mixture of (7b) and the lactam (2b) in the ratio *ca.* 1:9. Reaction of (6b) gave only 40% conversion at 80°C and 55% at 100°C with the carbonylation product (10b) preferred over (8b) with ratios of 75:25 at 80°C and 60:40 at 100°C.

Use of the basic phosphine $P(Cy)_3$ as ligand again led to increased formation of hydroformylation products as noted above. The ratio of (7b) and (2b) was now *ca.* 1:2 with only 40% conversion while the reaction of (6b) to give (8b) (*ca.* 75%) was faster than with PPh_3 giving 85% conversion at 100°C.

Reactions of 3-(prop-2-enylamino)propanamide (12)

The amide (12) was prepared by basic[24] or enzymatic[25] hydrolysis of the nitrile (3a). Although enzymatic hydrolysis was slow an excellent yield (92%) was obtained compared with basic hydrolysis (61%).



(12) Scheme 5 (13) (14)

Table 5. Effect of ligand variation on chemoselectivity for reactions of the amide (12)

Ligand PR_3	Product Distribution	
R	Hydroformylation (13)	Carbonylation (14)
Ph	40	60
Cy	95	5
n-Bu	>95	<5
o-Tol	15	85
BIPHEPHOS	> 95	< 5

Rhodium catalysed reactions of (12) with H_2/CO were carried out with a range of ligands as described above. The results (Table 5) showed that it was once again possible to influence the chemoselectivity in favour of the hydroformylation product (13) or the carbonylation product (14) as found for the diamino analogue (5a) (Scheme 5) but in this case, the use of BIPHEPHOS did not give complete control of chemoselectivity. The oxodiazabicyclononane (13) has potential for further functionalisation and conversion into interesting multi-ring heterocycles.

EXPERIMENTAL

General conditions were as described previously.[4b,8,26]

Alkenyl amines

The amines were purchased from Aldrich (prop-2-enylamine) or prepared from the corresponding alcohols.[25]

3-(Alkenylamino)propanenitriles (3,4)

These compounds were prepared by heating a mixture of the alkenylamine with prop-2-enenitrile at 34° for 20h (for 3 and 4) or up to 3 days (for 5 and 6).[14]

3-(Prop-2-enylamino)propanenitrile (3a) (92%) was prepared from prop-2-enenitrile and prop-2-enamine, b.p (oven) 50°/0.1mm (lit.[14] 85°/5mm). υ_{max} 3318s, 2917s, 2842s, 2248s, 1648m, 1464m, 1420m, 1117m, 997m, 923m cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.44, s, 1H, NH; 2.53, t, *J* 6.5 Hz, 2H and 2.92, t, *J* 6.5 Hz, 2H, H2, 3; 3.29, td, *J* 6.0, 1.4 Hz, 2H, H1'; 5.09-5.26, m, 2H, H3'; 5.87, ddt, *J* 17.1, 10.2, 6.0 Hz, 1H, H2'. ^{13}C n.m.r. δ(50 MHz) 18.34 (C2); 43.87, 51.17 (C1, 3'); 116.09 (C3'); 118.52 (C1); 135.80 (C2'). Mass Spectrum: *m/z* 110 (M, 2%), 83 (12), 70 (100), 68 (20), 54 (21).

3-(2-Methylprop-2-enylamino)propanenitrile (3b) (100%) b.p. (oven) 55°/0.08mm. (Found: 124.100±0.001. $C_7H_{12}N_2$ requires 124.100). υ_{max} 3568bm, 3334s, 3075m, 2917s, 2834s, 2248s, 1653s, 1460s, 1423s, 1373s, 1332m, 1242m, 1125s, 1055m, 899s, 770s, 704m cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.51, bs, 1H, NH; 1.75, s, 3H, CH_3; 2.52, t, *J* 6.1 Hz, 2H, and 2.88, t, *J* 6.0 Hz, 2H, H2, 3; 3.20, s, 2H, H1'; 4.88, m, 1H and 4.89, m, 1H, H3'. ^{13}C n.m.r. δ(50 MHz) 18.35 (C2); 20.15 (CH_3); 43.83, 54.52 (C1', 3); 110.95 (C3'); 118.57 (C1); 142.97 (C2'). Mass Spectrum: *m/z* 124(M-1, <1%), 97 (5), 83 (100), 54 (23).

3-(But-3-enylamino)propanenitrile (4a) (73%) b.p. (oven) 35°/0.07mm. υ_{max} 3314bs, 2930s, 2838s, 2247s, 1640s, 1474s, 1421s, 1359m, 1128s, 997s, 916s cm^{-1}. ^1H n.m.r. δ(400 MHz) 1.70, bs, 1H, NH; 2.26, qt, *J* 6.8, 1.3 Hz, 2H, H2'; 2.52, t, *J* 6.6 Hz, 2H, H2; 2.71, t, *J* 6.8 Hz, 2H, H1'; 2.92, t, *J* 6.6 Hz, 2H, H3; 5.08, m, 2H, H4'; 5.78, m, 1H, H3'. ^{13}C n.m.r. δ(100 MHz) 18.16 (C2); 33.66 (C2'); 44.46, 47.60 (C1', 3); 116.21 (C4'); 118.44 (C1); 135.58 (C3'). Mass Spectrum: *m/z* 122 (M-2, <1%), 83 (100), 68 (3) 54 (68).

3-(3-Methylbut-3-enylamino)propanenitrile (4b) (42%) b.p. (oven) 45°/0.08mm. (Found: 138.115±0.001. $C_8H_{14}N_2$ requires 138.116). υ_{max} 3314bw, 2936s, 2840s, 2248m, 1648s, 1458s, 1423m, 1375m, 1130s, 891s cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.46, bs, 1H, NH; 1.63, s, 3H, CH_3; 2.11, t, *J* 6.9 Hz, 2H and 2.42, t, *J* 6.7 Hz, 2H, H2, 2'; 2.65, t, *J* 6.9 Hz, 2H and 2.83, t, *J* 6.7 Hz, 2H, H1',3; 4.63, m, 1H and 4.69, m, 1H, H4'. ^{13}C n.m.r. δ (50MHz) 18.32 (C2); 21.86 (CH_3); 37.56 (C2'); 44.66, 46.32 (C1', 3); 111.49 (C4'); 118.49 (C1); 142.78 (C3'). Mass Spectrum: *m/z* 138(M, <1%), 83 (100), 54 (20).

N-Alkenyl-1,3-diaminopropanes (5,6)

These compounds were prepared by the $LiAlH_4$ reduction[13,27] of the above *N*-(alkenylamino)propanenitriles (3,4) using $Na_2SO_4 \cdot 10H_2O$ for workup.[28]

N-(Prop-2-enyl)-1,3-diaminopropane (5a) was obtained from 3-(prop-2-enylamino)propanenitrile (3a) as a yellow oil (70%). Kugelrohr distillation gave a colorless oil (48%), b.p. (oven) 75°/18mm (lit.[13] 66°/14mm). υ_{max} 3296bs, 2929s, 2183m, 1642s, 1595s, 1458m, 1111m cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.64, m, 2H, H2; 1.98, bs, 3H, NH, NH_2; 2.66, t, *J* 7.0 Hz, 2H and 2.75, t, *J* 7.0 Hz, 2H, H1, 3; 3.23, dt, *J* 6.0, 1.34 Hz, 2H, H1'; 5.04-5.22, m, 2H, H3'; 5.90, ddt, *J* 17.2, 10.2, 6.0 Hz, 1H, H2'. ^{13}C n.m.r. δ(50 MHz) 33.64 (C2); 40.34, 47.10, 52.48 (C1', 1, 3); 115.79 (C3'); 136.88 (C2'). Mass Spectrum: *m/z* 115 (M+1, <1%), 96 (6), 82 (27), 70 (100), 68 (40), 56 (66).

N-(2-Methylprop-2-enyl)-1,3-diaminopropane (5b) was obtained as a clear liquid (80%), b.p. (oven) 60°/13mm. (Found: 128.132±0.001. $C_7H_{16}N_2$ requires 128.131). υ_{max} 3287bs, 2932s, 2859s, 1654m, 1599w, 1458m, 1121m, 892m cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.58-1.69, m, 2H, H2; 1.74, s, 3H, CH_3; 2.27, bs, 3H, NH, NH_2; 2.64, t, *J* 6.9 Hz, 2H and 2.78, t, *J* 6.9 Hz, 2H, H1, 3; 3.16, s, 2H, H1'; 4.82, m, 1H and 4.86, m, 1H, H3'. ^{13}C n.m.r. δ(50 MHz) 20.77 (CH_3); 33.37 (C2); 40.49, 47.14 (C1, 3); 55.77 (C1'); 110.91 (C3'); 143.91 (C2'). Mass Spectrum: *m/z* 128 (M, 52%), 111 (24), 96 (57), 84 (100), 70 (98), 55 (99).

N-(But-3-enyl)-1,3-diaminopropane (6a) (95%), b.p.(oven) 85°/18mm. υ_{max} 3356bs, 2934s, 1639m, 1597m, 1458m, 1119m, 994m, 912m cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.50, bs, 3H, NH, NH_2; 1.63, m, 2H, H2; 2.25, m, 2H, H2'; 2.67, t, *J* 6.9 Hz, 4H and 2.76, t, *J* 6.9 Hz, 2H, H1, 1', 3; 5.0-5.14, m, 2H, H3'; 5.68-5.89, m, 1H, H4'. ^{13}C n.m.r. δ(50 MHz) 33.41, 33.88 (C2, 2'); 41.0, 47.26, 48.54 (C1, 3, 1'); 115.86 (C4'); 136.08 (C3'). Mass Spectrum: *m/z* 129 (M+1, 50%), 113 (11), 100 (60), 98 (18), 87 (100), 85 (38), 70 (78), 57 (100).

N-(3-Methylbut-3-enyl)-1,3-diaminopropane (6b) (40%), b.p. (oven) 65-75°/15mm. (Found: 142.147±0.001. $C_8H_{11}N_2$ requires 142.147). υ_{max} 3283bs, 2933s, 1648m, 1545m, 1457s, 1375m, 1124m, 887m cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.65, m, 2H, H2; 1.74, s, 3H, CH_3; 1.80, bs, 3H, NH, NH_2; 2.22, t, *J* 6.9 Hz, 2H, H2'; 2.65-2.80, m, 6H, H1, 3, 1'; 4.72, m, 1H and 4.78, m, 1H, H4'. ^{13}C n.m.r. δ(50 MHz) 22.27 (CH_3); 33.68 (C2); 38.01 (C2'); 40.49, 47.54, 47.72 (C3, 1, 1'); 111.45 (C4'); 143.58 (C3'). Mass Spectrum: *m/z* 143 (M+1, <1%), 98 (8), 87 (100), 84 (20), 70 (23), 56 (40).

Preparation of 3-(prop-2-enylamino)propanamide (12).

Finely powdered KOH (5.63g, 100 mmol) was addded to a stirred solution of *N*-(prop-2-enylamino)propanenitrile (3a) (3g, 27.3mmol) in *t*-butanol (30ml) and heated to reflux for 1h, cooled to ambient temperature and poured into an aqueous solution of NaCl (50ml). The aqueous solution was extracted with chloroform (50ml) and washed with further quantities of chloroform (2x25ml). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give a pale yellow oil (2.36g, 68%). Column chromatography (silica: 10% EtOH/EtOAc) gave *3-(prop-2-enylamino)propanamide* (12) as a pale yellow oil that crystallised as a low melting solid on extended cooling (2.11g, 61%), b.p (oven)125°/21mm. (Found: C, 55.8; H, 9.1; N, 21.5. $C_6H_{12}N_2O$ requires C, 56.2; H, 9.4; N, 21.9%). υ_{max} 3366s, 3190s, 2976m, 2832m, 1667s, 1412m, 1110m, 996m, 920m cm^{-1}. ^1H n.m.r. δ(200 MHz) 2.13, t, 2H, *J* 6.3 Hz, H2; 2.57, t, 2H, *J* 6.3 Hz, H1; 2.96, d, 2H, *J* 6.0 Hz, H1'; 4.85, m, 2H, H3'; 5.25, ddt, *J* 17.0, 10.2, 6.0 Hz, 1H, H2'. ^{13}C n.m.r. δ(50 MHz) 34.62 (C2); 44.12 (C1); 51.26 (C1'); 116.02 (C3'); 135.40 (C2'); 175.35 (CO). Mass Spectrum: *m/z* 128 (M, 54%), 111 (23), 87 (52), 70 (100), 68 (72), 56 (98).

The enzymatic hydrolysis followed was the general procedure of Turner and Parratt[25]. Nitrilase SP361[29] (1.07g) and *N*-(prop-2-enylamino)propanenitrile (3a) (0.3g, 2.73mmol) in 0.01M phosphate buffer were stirred gently (so not to create a vortex) in a thermostatically controlled oil bath at 30° for 8 days. The reaction mixture was filtered through a pad of Celite and the aqueous layer was concentrated to give a cream solid which was triturated with dichloromethane (2x50ml). Removal of the solvent gave the amide (12) as a low melting yellow solid (0.28g, 92%). Spectral data was identical to that given above.

Rhodium catalysed reactions with H_2/CO

The general procedure as described for the reaction of the *N*-propenyldiaminopropane (5a) was followed.

N-(prop-2-enyl)-1,3-diaminopropane (5a). The amine (5a) (0.3g, 2.6mmol), triphenylphosphine (13.3mg, 0.051mmol) and rhodium(II) acetate dimer (5.8mg, 0.013mmol) were dissolved in deoxygenated benzene (10ml) in a 100ml Parr autoclave which was then pressurised with H_2/CO (1:1 molar ratio, 400 p.s.i) and heated to 80° for 20h. The autoclave was cooled to ambient temperature and the solvent removed under vacuum to give a brown oil (0.39g). The ^1H n.m.r. and ^{13}C n.m.r. spectra of this oil showed a mixture of the bicyclic compound (7a) and the lactam (2a) in the ratio 40:60. Kugelrohr distillation gave 1,5-diazabicyclo[4.3.0]nonane (7a) as a clear oil (0.13g, 38%), b.p. (oven) 65-75°/18mm. (lit.[30] 60°/15mm). υ_{max} 3282bs, 2937s, 2786m, 1458m, 1167m, 1087m, 897m cm^{-1}. ^1H n.m.r. δ(400 MHz) 1.36-1.44, m, 1H, H7 or 8; 1.50, m, 1H, H3; 1.64, m, 1H, H7 or 8; 1.67, m, 1H, H3; 1.74-1.86, m, 1H, H7 or 8; 1.93-2.01, m, 1H, H7 or 8; 2.15, q, *J* 8.9 Hz, 1H, H9; 2.28, td, *J* 11.6, 3.1 Hz, 1H, H4; 2.68, td, *J* 12.8, 3.4 Hz, 1H, H2; 2.86, dd, *J* 9.2, 6.3 Hz, 1H, H6; 3.01, td, *J* 8.9, 2.2 Hz, 1H, H9; 3.11-3.13, m, 1H, H2; 3.2, m, 1H, H4. ^{13}C n.m.r. δ(100 MHz) 19.13 (C7 or 8); 26.07 (C3); 30.10 (C7 or 8); 45.59 (C2); 51.47 (C9); 51.79 (C4); 78.73 (C6). Mass Spectrum: *m/z* 126 (M, 46%), 125 (M-1, 85), 98 (94), 85 (81), 70 (100), 56 (58), 44 (33). Spectral data was in agreement with literature data.[30]

The distillation residue (0.15g) was mixed with acetic anhydride (0.32g, 3.0mmol) and refluxed for 10-15min. The reaction mixture was cooled, diluted by the addition of water (10ml) and refluxed for 15min to decompose any excess acetic anhydride. When cool, the mixture was extracted into dichloromethane (3x15ml). The organic phase was dried (Na_2SO_4), filtered, and concentrated. Column chromatography (alumina: 5% ethanol in ether) gave *N-(3-acetylaminopropyl)pyrrolidin-2-one* as a clear oil (0.15g, 31%). (Found: 184.121±0.002. $C_9H_{16}N_2O_2$ requires 184.121). υ_{max} 3422bs, 2936s, 2876m, 1654s, 1560m, 1438m, 1294m cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.62-1.75, m, 2H, H4; 1.96-2.14, m, 2H, H2'; 1.99, s, 3H, CH_3; 2.43, t, *J* 8.0 Hz, 2H, H3; 3.18, t, *J* 6.1 Hz, 2H, H5; 3.36, t, *J* 6.2 Hz, 2H and 3.41, t, *J* 7.0 Hz, 2H, H1', 3'. ^{13}C n.m.r. δ(50 MHz) 17.91 (C4), 23.30 (CH_3), 26.39 (C2'), 30.93 (C3), 35.48, 39.54, 47.36 (C1', 3', 5), 170.40, 176.00 ($\underline{C}OCH_3$, C2). Mass Spectrum: *m/z* 184 (M, 11%), 55 (4), 141 (5), 125 (6), 112 (100), 98 (80), 84 (20), 70 (72), 56 (47).

Authentic samples of the aminolactam (2a) and its *N*-acetyl derivative were prepared by the alkylation of 2-pyrrolidinone in DMF with 3-bromopropylamine hydrobromide[31] in the presence of sodium hydride followed by acetylation. Spectral data was in agreement with that reported above.

Reactions of (5a) with H_2/CO mixtures 9:1 and 1:9 were carried out as above with a total initial gas pressure of 400 p.s.i. Reactions with other ligands used the substrate: $[Rh(OAc)_2]_2$: ligand ratio of 200:1:4. BIPHEPHOS, a bidentate ligand, prepared as described by Buchwald[17] was used in the ratio 200:1:2.

N-(2-methylprop-2-enyl)-1,3-diaminopropane (5b). Reaction of the amine (5b) (0.3g, 2.3mmol) at 80° gave a brown oil (0.23g). The crude ^{13}C and ^1H n.m.r. spectra indicated the presence of starting material (10%), with the bicyclo compound (7b) and the lactam (2b) in the ratio 1:9. Kugelrohr distillation gave *8-methyl-1,5-diazabicyclo[4.3.0]nonane* (7b) as a clear oil (0.06g, 18%), b.p. (oven) 70°/15mm. (Found: 140.131±0.001. $C_8H_{16}N_2$ requires 140.131). υ_{max} 3362bs, 2957s, 1655m, 1560m, 1459m, 1325m cm^{-1}. ^1H n.m.r. δ(200 MHz) 0.87-1.20, m, 4H; 1.44-1.81, m, 4H; 2.20-2.42, m, 3H; 2.57-2.84, m, 2H; 2.91-2.96, m, 1H; 3.09-3.20, m, 2H. ^{13}C n.m.r. δ(50 MHz) 20.40 (CH_3); 25.84 (C3); 27.17 (C8); 38.62 (C7); 45.15, 51.59, 60.25 (C2, 4, 9); 77.84 (C6). Mass Spectrum: *m/z* 140 (M, 18%), 138 (60), 125 (10), 113 (31), 98 (49), 84 (58), 70 (97), 56 (100).

The residue was predominantly *N-(3-aminopropyl)-4-methylpyrrolidin-2-one* (2b). (Found: 156.126±0.001. $C_8H_{16}N_2O$ requires 156.126). υ_{max} 3366m, 3297m, 2929s, 2869s, 1684s, 1431m, 1269m cm^{-1}. ^1H n.m.r. δ(400 MHz) 1.12, d, *J* 6.8 Hz, 3H, CH_3; 1.65, m, 2H, H2'; 2.01, dd, *J* 16.3, 6.5 Hz, 1H, H3; 2.40-2.46, m, 1H, H4; 2.54, dd, *J* 16.3, 8.5 Hz, 1H, H3; 2.62, t, *J* 6.6 Hz, 2H, H3'; 2.94, dd, *J* 9.6, 5.8 Hz, 1H, H5; 3.35, m, 2H, H1'; 3.48, dd, *J* 9.5, 7.6 Hz, 1H, H5. ^{13}C n.m.r. δ(100 MHz) 19.57 (CH_3); 26.06 (C4); 30.41 (C2'); 38.61 (C3'); 39.07, 39.17 (C3, 1'); 54.08 (C5). Mass Spectrum: *m/z* 156 (M, 5%), 140 (13), 126 (29), 112(100), 98 (20), 84 (72), 70 (43), 56 (52).

A portion of the distillation residue from a separate reaction was acetylated as described above. Extensive chromatography (alumina: diethyl ether to 5% ethanol/ether) gave *N-(3-acetylaminopropyl)-4-methylpyrrolidin-2-one* as a pale yellow oil (32%). (Found: 198.137±0.002. $C_{10}H_{18}N_2O_2$ requires 198.137). υ_{max} 3423bs, 2964m, 2874m, 1655s, 1560m, 1493m, 1438m, 1376m, 1303m cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.36, d, *J* 6.6 Hz, 3H, CH_3; 1.65-1.73, m, 2H, H2'; 1.98, s, 3H, $COCH_3$; 2.07-2.11, m, 1H, H3; 2.43-2.52, m, 1H, H4; 2.53-2.64, m, 1H, H3; 2.98, dd, *J* 9.8, 5.7 Hz, 1H, H5; 3.18, m, 2H, H1'; 3.34, m, 2H, H3'; 3.52, dd, *J* 9.6, 7.7 Hz, 1H, H5. ^{13}C n.m.r. δ(50 MHz) 19.56 (CH_3); 22.94 (C4); 26.10 ($CO\underline{C}H_3$); 26.19 (C2'); 35.39 (C3'); 38.98, 39.11 (C1', 3); 54.26 (C5); 170.00, 174.90 (C2, $\underline{C}OCH_3$). Mass Spectrum: *m/z* 198 (M, 13%), 183 (3), 169 (11), 155 (5), 140 (9), 126 (100), 112 (55), 100 (30), 84 (51), 70 (21), 56 (40).

N-(But-3-enyl)-1,3-diaminopropane (6a). Reaction of the amine (6a) (0.3g, 2.3mmol) gave a brown oil (0.23g). The ^{13}C n.m.r. spectrum indicated an isomeric mixture (85:15) of 1,5-diazabicyclo[4.4.0]decane (8a) and *7-methyl-1,5-diazabicyclo[4.3.0]nonane* (9), together with products of carbonylation, *N*-(3-aminopropyl)piperidin-2-one (10a) and *N*-(3-aminopropyl)-3-methylpyrrolidin-2-one (11) (25:75). Kugelrohr distillation gave a clear oil consisting of the isomeric bicyclic amines (8a) and (9), (0.1g, 31%) b.p. (oven) 92°/15mm (lit.[32] for (8a) 86°/12-14mm). (Found: 140.131±0.001. $C_8H_{16}N_2$ requires 140.131). υ_{max} 3383bs, 2938s, 1654m, 1469m, 1376m, 1324w, 1294m, 1260m, 1136m cm^{-1}. ^1H n.m.r. δ(200 MHz) (for (8a)) 1.19-1.48, m, 1H; 1.51-1.88, m, 7H; 1.97-2.11, m, 1H; 2.21, td, *J* 11.8, 3.3 Hz, 1H; 2.58-2.76, m, 3H; 2.85-2.95, m, 1H; 3.02-3.13, m, 1H. ^{13}C n.m.r. δ(50 MHz) Major isomer (8a): 23.96, 25.22, 27.36, 32.98 (C3, 7, 8, 9); 44.92 (C2); 54.94, 54.99 (C4, 10); 76.65 (C6). Minor isomer (9): 17.34 (CH_3); 25.93, 28.22 (C3, 7); 37.51 (C8); 45.31, 50.07, 51.94 (C2, 4, 9); 85.01 (C6). Mass spectrum: *m/z* 140 (M, 7%), 138 (68), 137 (100), 127 (13), 123 (15), 113 (62), 98 (35), 82 (49), 70 (37), 55 (72).

The distillation residue was reacted with phthalic anhydride[33] and the resulting phthalimide derivatives of the lactams (10a) and (11) chromatographed (silica: ethyl acetate/light petroleum 3:2) to give *3-methyl-N-(3-phthalimidopropyl)pyrrolidin-2-one* (0.07g, 10%). (Found: C, 66.8; H, 6.6; N, 10.0. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8%). υ_{max} 3463bm, 2935m, 2873m, 1771m, 1711s, 1677s, 1466m, 1437m, 1399s, 1376m, 1300w, 1032w, 722s cm^{-1}. ^1H n.m.r. δ(200 MHz, d_6-acetone) 1.08, d, *J* 6.9 Hz, 3H, CH_3; 1.51-1.69, m, 1H, H3; 1.91, p, *J* 7.2 Hz, 2H and 2.17-2.41, m, 2H, H4, 2'; 3.28-3.40, m, 4H and 3.63, m, 2H, H5, 1', 3'; 7.85, s, 4H, ArH. ^{13}C n.m.r. δ (50 MHz, d_6-acetone) 16.47 (CH_3); 26.91, 28.01 (C2', 4); 37.17 (C3); 36.15, 40.62, 45.20 (C5, 1', 3'); 123.63 (ArCH); 133.11 (ArC); 134.90 (ArCH); 168.70, 177.12 (C2, ArC=O). Mass Spectrum: *m/z* 287 (M+1, 3%), 286 (M, 14), 258 (2),188 (4), 160 (18), 138 (13), 130 (15), 126 (100), 113 (53), 98 (32), 84 (90), 76 (20), 56 (30) followed by *N*-(3-phthalimidopropyl)piperidin-2-one (0.05g, 7.5%). υ_{max} 3463bw, 1770m, 1711s, 1634s, 1398m, 1356w, 720m cm^{-1}. ^1H n.m.r. δ(200 MHz, d_6-acetone) 1.84-1.74, m, 4H and 1.88-1.99, m, 2H, H4, 5, 2'; 2.22, t, 2H, *J* 6.0 Hz, H3; 3.45-3.30, m, 4H and 3.65, t, *J* 7.2 Hz, 2H, H6, H1', H3'; 7.85, s, 4H, ArH. ^{13}C n.m.r. δ(50 MHz, d_6-acetone) 22.13, 23.99, 26.80 (C4, 5, 2'); 32.88 (C3); 36.31, 44.83, 48.16 (C6, 1', 3'); 123.63 (ArCH); 133.14(ArC); 134.89 (ArCH); 168.76, 169.39 (C2, ArC=O). Mass spectrum: *m/z* 287 (M+1, 4%), 286 (M, 12), 230 (5), 188 (6), 160 (30), 126 (100), 113 (63), 98 (35), 76 (36), 70 (18), 56 (52).

Reactions using BIPHEPHOS (25mg, 0.032mmol) as ligand gave the diazabicyclodecane (8a) as the sole product (>95%) with identical ^1H and ^{13}C n.m.r. data to those reported above.

N-(3-Methylbut-3-enyl)-1,3-diaminopropane (6b). Reaction of the amine (6b) (0.3g, 2.1mmol) at 80° gave a yellow oil (0.28g) whose ^{13}C and ^1H n.m.r. spectra indicated starting material (6b) (*ca* 60%) and a mixture of 8-methyl-1,5-diazabicyclo[4.4.0]decane (8b) and *N*-(3-aminopropyl)-4-methylpiperidin-2-one (10b) in the ratio 1:3. The ratio of diasteroisomers of (8b) was estimated to be 9:1 from the ^{13}C n.m.r. spectra. Kugelrohr distillation gave the major stereoisomer of *8-methyl-1,5-diazabicyclo[4.4.0]decane* (8b) as a low melting white solid (0.08g, 25%) (Found: 154.145±0.002. $C_9H_{18}N_2$ requires 154.147) b.p. (oven) 70°/15mm. υ_{max} 3360bs, 2927s, 1648m, 1560m, 1458m, 1376m, 1309m cm^{-1}. ^1H n.m.r. δ(400 MHz) 0.89, d, *J* 6.3 Hz, 3H, CH_3; 0.95, m, 1H, H7; 1.26, apparent qd, *J* 12.6, 3.9 Hz, 1H, H9; 1.55, m, 1H, H3; 1.58, m, 1H, H8; 1.61, m, 1H, H9; 1.73, m, 1H, H7; 1.78, m, 1H, H3; 2.06, td, *J* 12.0, 2.6 Hz, 1H, H10; 2.17, dd, *J* 12.0, 3.0 Hz, 1H, H2; 2.61, m, 1H, H4; 2.68, m, 1H, H6; 2.70, m, 1H, H10; 2.92, apparent dp, *J* 11.4, 2.1 Hz, 1H, H2; 3.06, ddt, *J* 13.6, 4.4, 1.8 Hz, 1H, H4. ^{13}C n.m.r. δ(100 MHz) 21.94 (CH_3); 27.56 (C3); 30.83 (C8); 33.87 (C9); 41.68 (C7); 44.96 (C4); 54.76 (C10); 54.92 (C2); 77.04 (C6). Mass Spectrum: *m/z* 154 (M, 11%), 153 (22), 137 (32), 127 (22), 112 (27), 98 (48), 87 (50), 84

(79), 70 (100), 56 (99). Further Kugelrohr distillation gave a mixture of the stereoisomers as a clear oil (0.15g, 46%), b.p. (oven) 100°/15mm. Chromatography of the residue failed to recover the lactam product (10b). (^{13}C n.m.r. δ 167.5).

3-(Prop-2-enylamino)propanamide (12). Reaction of the amide (12) (0.3 g, 2.34mmol), at 80° gave a yellow oil (0.32g) shown to be a mixture of the bicyclic compound (13) and the lactam (14) in the ratio 40:60 by ^{1}H and ^{13}C n.m.r. spectroscopy. Column chromatography on the benzene soluble fraction of the oil (0.12g) (alumina: 20% EtOH/EtOAc) gave *4-oxo-1,5-diazabicyclo[4.3.0]nonane* (13) as a clear oil (0.05g, 15%). (Found: 140.095±0.001. $C_7H_{12}N_2O$ requires 140.095) υ_{max} 3395s, 2958m, 1649s, 1467m, 1407m, 1359m, 1337m, 1310m cm^{-1}. ^{1}H n.m.r. δ(200 MHz) 1.68-1.81, m, 1H, H7; 1.86-2.01, m, 2H, H3; 2.05-2.25, m, 2H, H7, 8; 2.58, m, 1H, H8; 2.77-2.96, m, 2H, H2; 3.20, m, 2H, H9; 4.58, dd, *J* 5.3, 1.6 Hz, 1H, H6; 7.67, bs, 1H, NH. ^{13}C n.m.r. δ(50 MHz) 21.82 (C3); 29.70 (C8); 31.49 (C7); 42.85 (C9); 47.46 (C2); 72.02 (C6); 171.03 (C4). Mass spectrum: *m/z* 140 (M, 98%), 139 (100), 112 (90), 97 (45), 85 (43), 69 (51), 57 (67).

The remaining chloroform soluble products (0.20g) were purified by preparative high performance liquid chromatography (Deltapak C18 - 100A°, 19mm x 30cm, 15μ, 50% CH_3CN/H_2O to 100% CH_3CN over 30min) to give *N-(2-carbamoylethyl)pyrrolidin-2-one* (14) as a tan solid (0.04g, 11%) (Found: 156.090±0.001. $C_7H_{12}N_2O_2$ requires 156.089). υ_{max} (KBr) 3358s, 3171m, 2952w, 1667s, 1419m, 1293m, 677m cm^{-1}. ^{1}H n.m.r. δ(200 MHz) 1.97, m, 2H, H4; 2.31, t, *J* 8.0 Hz, 2H and 2.44, t, *J* 6.6 Hz, 2H, H3, 2'; 3.40, t, *J* 7.0 Hz, 2H and 3.50, t, *J* 6.6 Hz, 2H, H5, 1'. ^{13}C n.m.r. δ(50 MHz) 17.70 (C4); 30.69, 33.69, 38.94, 47.59 (C3, 5, 1', 2'); 173.61 (CO); 175.32 (CO). Mass spectrum: *m/z* 156 (M, 12%), 139 (52), 111 (100), 98 (46), 84 (38), 70 (82), 56 (64).

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