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Synthesis of Substituted α-Methylene Lactams by Rhodium Catalysed Carbonylation of Acetylenic Amines

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Abstract: Reactions of γ- and β-aminoalkynes, (2) and (5) with hydrogen and carbon monoxide in the presence of rhodium catalysts give substituted α-methylene-2-piperidinones (7) and 2-pyrrolidinones (11).

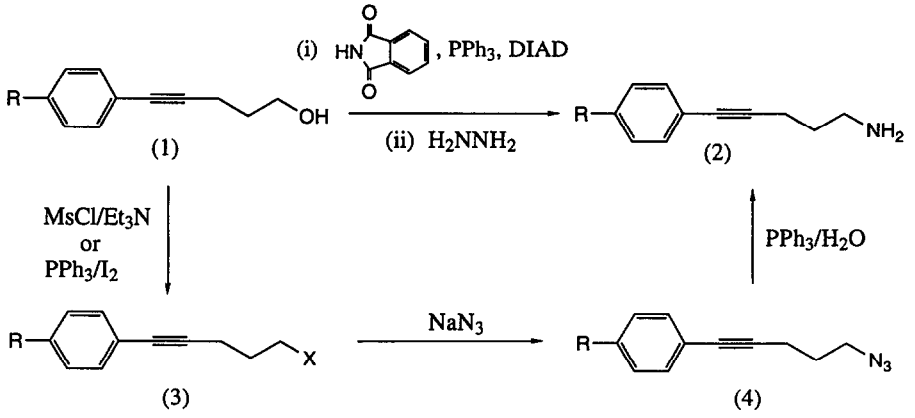
INTRODUCTION

Rhodium-catalysed reactions of 1-aminopent-4-enes with H_2/CO have been shown to give 2-piperidinone derivatives in high yield under mild conditions.[1] It was thus of interest to study related reactions of the corresponding alkynes, 1-aminopent-4-ynes. Although alkynes are normally less reactive than the corresponding alkenes,[2] work in this laboratory has shown that substituted propargylamines react smoothly with H_2/CO in the presence of rhodium catalysts.[3] In addition, the reaction of 4-phenylbut-3-ynylamine has been studied for comparison with both its lower and higher homologues.

RESULTS AND DISCUSSION

Preparation of alkynylamines

5-Arylpent-4-yn-1-ols (1) were prepared by established literature procedures and converted into the corresponding primary amines (2). This conversion involved either the Mitsunobu protocol established by Hegedus[4] or a sequence involving azido intermediates and their reduction with Ph_3P/H_2O[5] (Scheme 1).



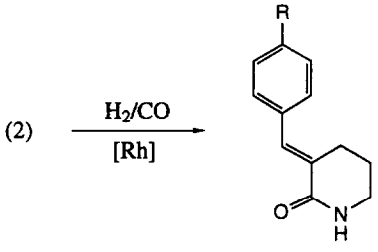
(a) X = OMs (b) X = I

Scheme 1

4-Phenylbut-3-ynylamine (5)[6], pent-4-ynylamine (6; R=H) and the alkyl substituted alkyne non-4-ynylamine (6; R=Bu) were prepared by analogous methods.

Reactions with H_2/CO

Reactions of the γ-aminoalkynes (2) with H_2/CO in the presence of$[Rh(OAc)_2]_2/PPh_3$ in either benzene or ethyl acetate gave substituted methylene 2-piperidinones (7) as the major products. Reactions of arylalkynes (2; R=Ph, p-MeC_6H_4) were highly regio- and stereo-selective giving the lactams (7; R=Ph, p-MeC_6H_4) as the only products. The homogeneity of the products was shown by the ^1H and ^{13}C n.m.r. spectra of the crude reaction mixtures. The stereochemistry of the substituted methylene 2-piperidinones has been established previously the ^1H n.m.r. spectrum of our product from the reaction of 5-phenylpent-4-ynylamine (2; R=H) was identical with that reported for the E-isomer.[7]Chromatography gave pure samples of these compounds in 40-50% yield. Reactions of the 4-methoxy and 4-cyano compounds (2; R=*p*-$MeOC_6H_4$, *p*-NCC_6H_4) were not as clean but the lactams (7) could still be isolated in moderate to low yields (*ca.* 30% and 10%, respectively). The decrease in yield from reactions of the *p*-cyano- and *p*-methoxy compounds relative to that obtained for the phenyl compound is not clearly understood. Both of these reactions gave significant quantities of intractable material, apparently of high molecular weight and it is possible that both electron donating and electron withdrawing substituents promote oligomerisation or polymerisation reactions.



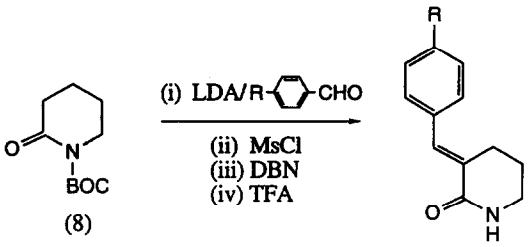
(7)

Reactions were carried out in benzene or ethyl acetate using the substrate (2), $[Rh(OAc)_2]_2$ and PPh_3 in a ratio of 200:1:4 and H_2/CO (1:1) at an initial pressure of 2760 kPa (400 psi) for 20 h at 80-90°C.

The highly regio- and stereoselective carbonylation reactions contrast with reactions of propargylamines which under similar conditions gave products resulting from hydroformylation rather than carbonylation.[3] This unexpected change in the reactivity pattern contrasts with analogous rhodium-catalysed reactions of α-, β- and γ-alkenylamines which all gave products resulting from carbonylation reactions.[1]

Preparation of authentic samples of 2-piperidinones (7)

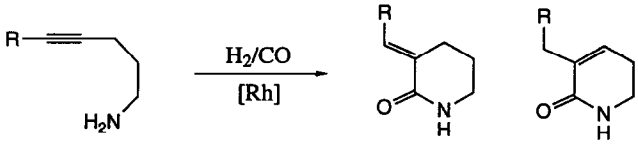
Authentic samples of the phenyl and *p*-tolyl compounds (7; R=Ph, p-MeC_6H_4) were prepared by reactions of N-acetyl-2-piperidinone with the appropriate arylaldehyde in *ca.* 30% yield.[7] Samples of the *p*-cyano and *p*-methoxy compounds were obtained by an improved procedure based on an aldol/dehydration sequence using N-Boc protected 2-piperidinone (8)[8] (Scheme 2). Again the *p*-cyano compound was obtained in the lower yield (34% compared to 63%).



Scheme 2

Reaction of non-4-ynylamine (6; R=Bu) with H_2/CO

The butyl-analogue (6; R=Bu) of the arylalkynylamines (2) reacted more slowly and a reaction for 20 h at 90°C in benzene gave recovered amine (50%) together with a mixture of the lactams (9; R=Bu) and (10; R=Bu) in ratio *ca.* 3:1. A pure sample of the methylene lactam (9; R=Bu) was prepared by the aldol/dehydration sequence described above (80%). This compound was shown to partially isomerise to the endocyclic isomer (10; R=Bu) under the conditions described above ($[Rh(OAc)_2]_2$, PPh_3, H_2/CO) or on heating in solution with a catalytic amount of rhodium(III) chloride. Further evidence that the exocyclic lactam (9; R=Bu) was the product of kinetic control came from a reaction with H_2/CO carried out in THF from which samples were taken after 20, 48 and 86 hours. The ratio of (9; R=Bu) : (10; R=Bu) decreased from 20 : 1 to 3 : 1 to 1 : 1 over this period.

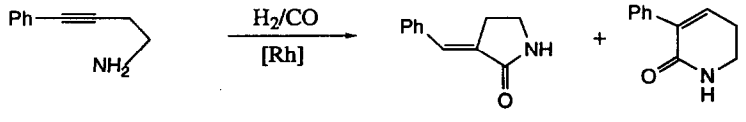


R = H or Bu

Reaction of pent-4-ynylamine (6; R=H) in benzene for 20 h at 90° gave recovered amine (*ca.* 50%), an intractable red-brown residue and a small amount of material (*ca.* 5-10%) whose ^1H n.m.r. spectrum, I.R. and mass spectrum were consistent with literature values for 3-methylene-2-piperidinone (9; R=H).[9] Reaction in ethyl acetate gave mainly pent-4-ynylacetamide (25%) together with polymeric material and only a trace of the piperidinone. The lack of reactivity of these unsubstituted or alkyl substituted γ-acetylenic amines relative to their aryl counterparts is similar to that previously reported for reactions of substituted propargylamines.[3]

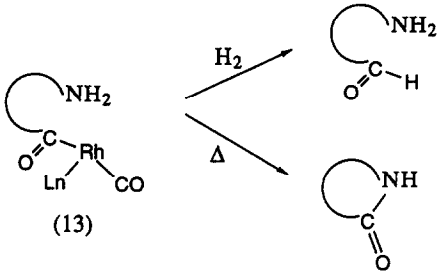
Reaction of 4-phenylbut-3-ynylamine (5) with H_2/CO

Reaction of 4-phenylbut-3-ynylamine (5) with H_2/CO was also examined A mixture of the two regioisomeric lactams (11) and (12) was formed in ratio *ca.* 3:2 in good yield (80%). Thus carbonylation was again the preferred reaction. The competitive formation of 5- and 6-membered lactams was also noted in reactions of related alkenamines.[1]



Mechanistic comments

A wide range of unsaturated amines and amides has now been reacted with H_2/CO in the presence of rhodium catalysts.[1,3,10,11] The products of these reactions can be interpreted as resulting from either initial hydroformylation or carbonylation reactions. This divergence of reaction pathways arises because in some unsaturated amines the amine nitrogen competes favourably with hydrogen in cleavage of the intermediate acylrhodium complex (13).



(13)

Hydroformylation, i.e. reaction with hydrogen occurs where the nitrogen atom is of low nucleophilicity, e.g. anilines[10] or where nitrogen coordination to rhodium is associated with a high degree of ring strain, e.g. in reactions of propargylamines.[3]

EXPERIMENTAL

General conditions are as described previously.[1,10]

Alkynols

5-Phenylpent-4-yn-1-ol (1; R=H) (95%) b.p. (oven) 150°/1 mm (lit.,[12] 160°/3 mm) was prepared from phenylacetylene and trimethylene oxide[12].

5-(4-Methylphenyl)pent-4-yn-1-ol (1; R=Me) (79%) was prepared by the same method[12] m.p. 38-39° (Found: C, 82.2; H, 8.0. $C_{12}H_{14}O$ requires C, 82.7, H, 8.1%). ν_{max} 3212s, 2220w, 1509m, 1067s, 1031m, 819s cm^{-1}. ^1H n.m.r. (200 MHz) 1.56, bs, 1H, OH; 1.86, tt, J 6.9, 6.2, Hz, 2H, H2; 2.33, s, 3H, CH_3; 2.53, t, J 6.9 Hz, 2H, H3; 3.83, t, J 6.2 Hz, 2H, H1; 7.09, d, J 8.2 Hz, 2H and 7.28, d, J 8.2 Hz, 2H, ArH. ^{13}C n.m.r. δ(50 MHz) 16.00 (C2); 21.38 (CH_3); 31.38 (C3); 61.90 (C1); 81.18, 88.44 (C4,5); 120.56 (ArC); 128.96, 131.38 (ArCH); 137.67 (ArC). Mass spectrum: m/z 174 (M, 47%), 159(42), 141(59), 131(35), 129(85), 128(100), 127(37), 119(26), 118(63), 117(30), 116(23), 115(85), 105(36), 91(37), 77(27).

5-(4-Methoxyphenyl)pent-4-yn-1-ol (1; R=OMe) (78%) was prepared from the Pd/Cu-catalysed coupling of 4-iodomethoxybenzene and 4-pentyn-1-ol.[13] B.p. 170°/10 mm, m.p. 39-40°. (Found: 190.099±0.002. $C_{12}H_{14}O_2$ requires 190.0994). ν_{max} 3197m, 1608m, 1512s, 1291m, 1246s, 1174m, 1070w, 1032m, 838m cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.84, tt, J 6.9, 6.2 Hz, 2H, H2; 2.05, s, 1H, OH; 2.51, t, J 6.9 Hz, 2H, H3; 3.78, s, 3H, OCH_3; 3.80, t, J 6.2 Hz, 2H, H1; 6.81, d, J 8.7 Hz, 2H and 7.32, d, J 8.7 Hz, 2H, ArH. ^{13}C n.m.r. δ(50 MHz) 15.90 (C2); 31.37 (C3); 55.16 (OCH_3); 61.71 (C1); 80.76, 87.65 (C4,5); 113.75 (ArCH); 115.76 (ArC); 132.79 (ArCH): 159.00 (ArC). Mass spectrum: m/z 190(M, 75%), 189(40), 173(23), 159(25), 157(33), 147(35), 146(25), 145(100), 144(32), 135(48), 134(95), 133(31), 128(44), 127(48), 121(59), 115(90), 102(48), 91(28).

4-(5-Hydroxypent-1-ynyl)benzonitrile (1; R=CN) (85%) was prepared as above from 4-bromobenzonitrile,[13] m.p. 52-53° (Found: 185.084±0.002. $C_{12}H_{11}NO$ requires 185.0840). ν_{max} 3316m, 2227s, 1604m, 1500m, 1054m, 838s cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.87, tt, J 7.0, 6.2 Hz, 2H, H4'; 2.57, t, J 7.0 Hz, 2H, H3'; 2.93, bs, 1H, OH; 3.79, t, J 6.2 Hz, 2H, H5'; 7.43, d, J 8.5 Hz, 2H and 7.56, d, J 8.5 Hz, 2H, ArH. ^{13}C n.m.r. δ(50 MHz) 15.74 (C4'); 30.87 (C3'); 60.86 (C5'); 79.41, 94.62 (C1',2'); 110.38 (ArC); 118.32 (CN); 128.64 (ArC); 131.65, 131.80 (ArCH). Mass spectrum: m/z 185(M, 28%), 184(27), 170(20), 167(35), 166(100), 140(74), 139(32), 129(43), 127(40), 114(22), 113(22).

4-Phenylbut-3-yn-1-ol (86%) was prepared from phenylacetylene and ethylene oxide,[14] b.p. (oven) 130°/0.3 mm (lit.,[14] 100°/0.2 mm).

Alkynylamines

5-Phenylpent-4-ynylamine (2; R=H) (74%) was prepared from the corresponding alcohol using the Mitsunobu protocol developed by Hegedus,[4] b.p. (oven) 100°/0.3 mm (lit.,[6] 67°/0.025 mm) (Found: C, 83.2; H, 8.2; N, 9.0. Calc. for $C_{11}H_{13}N$, C, 83.0; H, 8.2; N, 8.8%).

5-(4-Methylphenyl)pent-4-ynylamine (2; R=Me) (57%) was prepared as above,[4] b.p. (oven) 120°/0.2 mm, (Found: C, 83.1; H, 8.5; N, 7.9. $C_{12}H_{15}N$ requires C, 83.2; H, 8.7; N, 8.1%). ν_{max} 3374bm, 2225w, 1509s, 1434m, 817s cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.19, bs, 2H, NH_2; 1.73, tt, J 7.0 Hz, 2H, H2; 2.33, s, 3H, CH_3; 2.47, t, J 7.0 Hz, 2H, H3; 2.87, t, J 7.0 Hz, 2H, H1; 7.08, d, J 8 Hz, 2H and 7.28, d, J 8 Hz, 2H, ArH. ^{13}C n.m.r. δ(50 MHz) 16.84 (C2); 21.37 (CH_3); 32.50 (C3); 41.30 (C1); 80.90, 88.71 (C4, 5); 120.71 (ArC); 128.92, 131.35 (ArCH); 137.52 (ArC). Mass spectrum: m/z 174 (M+1, 29%), 173 (M, 81), 172(100), 156(60), 141(54), 129(47), 128(54), 115(44), 82(21).

Another sample was prepared from the alcohol (1; R=Me) via the mesylate (3a; R=Me) and the azide (4; R=Me) in 63% overall yield.

4-Phenylbut-3-ynylamine (5) (74%) was prepared as above,[4] b.p. (oven) 130°/2 mm (lit.,[15] 87°/1 mm) (Found: C, 82.7; H, 7.7; N, 9.8. Calc. for $C_{10}H_{11}N$, C, 82.7, H, 7.6; N, 9.7%). ^{13}C n.m.r. δ(50 MHz) 24.26 (C2); 40.96 (C1); 81.75, 87.68 (C3,4); 123.39 (ArC); 127.51, 128.00, 131.35 (ArCH).

5-(4-Methoxyphenyl)pent-4-ynylamine (2; R=OMe) was prepared from the alcohol (1; R=OMe) via the iodide (3b; R=OMe)[16] and the azide (4; R=OMe).[5]

5-Iodo-1-(4-methoxyphenyl)pent-1-yne (3b; R=OMe) (75%) b.p. (oven) 170°/0.1 mm, (Found: C, 47.8; H, 4.4. $C_{12}H_{13}IO$ requires C, 48.0; H, 4.4%). ^1H n.m.r. δ(200 MHz) 2.07, tt, J 6.8, 6.6 Hz, 2H, H4; 2.54, t, J 6.6 Hz, 2H, H3; 3.36, t, J 6.8 Hz, 2H, H5; 6.81, d, J 8.9 Hz, 2H and 7.33, d, J 8.9 Hz, 2H, ArH. ^{13}C n.m.r. δ(50 MHz) 5.53 (C5); 20.42 (C4); 32.22 (C3); 55.20 (OCH_3); 81.38, 86.11 (C1,2); 113.78 (ArCH); 115.61 (ArC); 132.86 (ArCH); 159.11 (ArC).

5-Azido-1-(4-methoxyphenyl)pent-1-yne (4; R=OMe) (98%) b.p.(oven) 150°/0.1 mm (Found: C, 66.9; H, 6.1; N, 19.3. $C_{12}H_{13}N_3O$ requires C, 67.0; H, 6.1; N, 19.5%). ν_{max} 2100s, 1607m, 1510s, 1290s, 1247s, 1173m, 1033m, 832m cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.84, tt, J 6.8, 6.7 Hz, 2H, H4; 2.50, t, J6.8 Hz, 2H, H3; 3.45, t, J 6.7 Hz, 2H, H5; 6.81, d, J 8.6 Hz, 2H and 7.33, d, J 8.6, 2H, ArH. ^{13}C n.m.r. δ(50 MHz) 16.47 (C4); 27.78 (C3); 50.05 (C5); 54.91 (OCH_3); 81.17, 86.37 (C1,2); 113.62 (ArCH); 115.47 (ArC); 132.68 (ArCH); 159.00 (ArC). Mass spectrum: m/z no M, 185(47%), 159(100), 144(22), 116(22), 115(35).

5-(4-methoxyphenyl)pent-4-ynylamine (2; R=OMe) (82%) was prepared by reduction of the azide[5] b.p. (oven) 150-160°/0.1 mm (Found: C, 76.3; H, 7.8. $C_{12}H_{15}NO$ requires C, 76.2; H, 8.0%). ν_{max} 3374bs, 2934s, 2837s, 1607s, 1569m, 1510s, 1464s, 1442s, 1289s, 1247s, 1173s,1107m, 1033s, 833s cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.78, p, J 7.0 Hz, 2H, H2; 2.48, t, J 7.0 Hz, 2H, H3; 2.50, bs, 2H, NH_2; 2.91, t, J 7.0 Hz, 2H, H1; 3.80, s, 3H, OCH_3; 6.81, d, J 8.8 Hz, 2H and 7.32, d, J 8.8 Hz, 2H, ArH. ^{13}C n.m.r. δ(50 MHz) 16.81 (C2); 32.28 (C3); 41.18 (C1); 55.18 (OCH_3); 80.64, 87.76 (C4,5); 113.75 (ArCH); 115.91 (ArC); 132.79 (ArCH); 158.99 (ArC). Mass spectrum: m/z 189(M, 49%), 188(80), 174(38), 172(100), 158(34), 157(64), 145(45), 129(37), 128(62), 127(39), 121(31), 115(75), 102(52), 91(31), 89(35), 77(77).

4-(5-aminopent-1-ynyl)benzonitrile (2; R=CN) was prepared via the iodide and azide.

5-Iodo-1-(4-cyanophenyl)pent-1-yne (3b; R=CN) (89%) b.p. (oven) 160°/0.1 mm (Found: C, 48.4; H, 3.4; N, 4.7. $C_{12}H_{10}IN$ requires C, 48.8; H, 3.4; N, 4.7%). ^1H n.m.r. δ(200 MHz) 2.10, p, J 6.7 Hz, 2H, H4'; 2.60, t, J 6.7 Hz, 2H, H3'; 3.35, t, J 6.7 Hz, 2H, H5'; 7.46, d, J 8.2 Hz, 2H and 7.58, d, J 8.2 Hz, 2H, ArH. ^{13}C n.m.r. δ(50 MHz) 5.05 (C5'); 20.24 (C4'); 31.39 (C3'); 80.07, 92.69 (C1',2'); 110.69 (ArC); 118.12 (CN); 128.12 (ArC); 131.59, 131.78 (ArCH).

4-(5-Azidopent-1-ynyl)benzonitrile (4; R=CN) (84%) (Found: C, 86.1; H, 4.9; N, 26.9. $C_{12}H_{10}N_4$ requires C, 68.6; H, 4.8; N, 26.7%). ν_{max} 2935w, 2227s, 2100s, 1604m, 1501m, 1255m, 840s cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.89, tt, J 6.9, 6.6 Hz, 2H, H4'; 2.57, t, J 6.9 Hz, 2H, H3'; 3.48, t, J 6.6 Hz, 2H, H5'; 7.46, d, J 8.3 Hz, 2H and 7.58, d, J 8.3 Hz, 2H, ArH. ^{13}C n.m.r. δ(50 MHz) 16.27 (C4'); 27.11 (C3'); 49.65 (C5'); 79.76, 92.98 (C1',2'); 110.51 (ArC); 117.96 (CN); 127.99 (ArC); 131.39, 131.58 (ArCH). Mass spectrum: m/z 211 (M+1, 5%), 182(11), 181(28), 167(15), 155(23), 154(100), 153(30), 140(38), 127(40).

4-(5-aminopent-1-ynyl)benzonitrile (2; R=CN) (95%) b.p. (oven) 150°/0.4 mm (Found: 184.100±0.002. $C_{12}H_{12}N_2$ requires 184.100). ν_{max} 3378bm, 2939s, 2861s, 2226s, 1604s, 1500s, 840s cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.79, tt, J 7.0, 6.9 Hz, 2H, H4'; 2.10, bs, 2H, NH_2; 2.53, t, J 7.0 Hz, 2H, H3'; 2.90, t, J 6.9 Hz, 2H, H5'; 7.45, d, J 8.6 Hz, 2H and 7.57, d, J 8.6 Hz, 2H, ArH. ^{13}C n.m.r. δ(50 MHz) 16.69 (C4'); 31.79 (C3'); 40.83 (C5'); 79.42, 94.69 (C1',2') 110.52 (ArC); 118.35 (CN); 128.66 (ArC); 131.65, 131.82 (ArCH). Mass spectrum: m/z 185(M+1, 32%), 184(M, 83), 183(100), 167(22), 166(34), 156(18), 140(26), 117(27), 116(73), 68(21).

Non-4-ynylamine (6; R=Bu) was prepared from 1-hexyne by the method of McGrane[6] (52%), b.p. (oven) 120°/20 mm. ^1H and ^{13}C n.m.r. spectra were identical with literature values.[6]

Pent-4-ynylamine (6; R=H) was prepared from the corresponding alcohol using the method of Hegedus[4] (60%) b.p. (oven) 150° (lit.[17] 124°). ^1H n.m.r. δ(200 MHz) 1.18, bs, 2H, NH_2; 1.67, p, J 7.0 Hz, 2H, H2; 1.96, t, J 2.7 Hz, 1H, H5; 2.27, td, J 7.0, 2.7 Hz, 2H, H3; 2.82, t, J 6.9 Hz, 2H, H1. ^{13}C n.m.r. δ(50 MHz) 15.49 (C2); 31.71 (C3); 40.66 (C1); 68.31 (C5); 83.63 (C4).

Reactions with H_2/CO

(E)-3-Phenylmethylene-2-piperidinone (7; R=H). In a typical reaction rhodium(II) acetate dimer (0.003 g, 0.0069 mmol), triphenylphosphine (0.0072 g, 0.0276 mmol) and 5-phenylpent-4-ynylamine (2; R=H) (0.22 g, 1.38 mmol) in ethyl acetate (10 ml) were reacted with H_2/CO (400 psi) at 90° for 20 h. The ^1H n.m.r. spectrum of the crude product showed lactam (7; R=H) with *ca.* 10% of the acetamide of (1). Column chromatography on alumina with ethyl acetate gave the lactam (7; R=H) (48%), m.p. 152-154°

(lit.,[7] 160-161°). (Found: C, 77.4; H, 6.9; N, 7.2. Calc. for $C_{12}H_{13}NO$, C, 77.0; H, 7.0; N, 7.5%). The ^1H and ^{13}C n.m.r. spectra were identical with a sample prepared by a literature method.[7]

A reaction in benzene at 90° for 20 h also gave the lactam (7; R=H) as the major product but in lower yield (40%).

(E)-3-(4-Methylphenyl)methylene-2-piperidinone (7; R=Me) was obtained from reaction of the amine (2; R=Me) (40%) and was identical to a sample prepared by the literture method,[7] m.p. 182-184° (Found: C, 77.4; H, 7.8; N, 6.7. $C_{13}H_{15}NO$ requires C, 77.6; H, 7.5; N, 7.0%). ν_{max} 1667s, 1613m, 1338m, 1138w, 823w cm^{-1}. ^1H n.m.r. δ(300 MHz), 1.86, p, J 6.0 Hz, 2H, H5; 2.37, s, 3H, CH_3; 2.81, m, 2H, H4; 3.42, t, J 5.8 Hz, 2H, H6; 7.19, d, J 8.0 Hz, 2H and 7.30, d, J 8.0 Hz, 2H, ArH; 7.4, bs, 1H, NH; 7.78, bs, 1H, HC=. ^{13}C n.m.r. δ(50 MHz) 21.27 (CH_3); 22.97, 26.25 (C4,5); 41.94 (C6); 128.76 (ArC) 128.98, 129.82 (ArCH); 132.90 (ArC); 135.55 (CH=); 138.15 (C3); 167.01 (C2). Mass spectrum: m/z 201(M, 29%), 172(7), 143(9), 128(13), 115(16).

(E)-3-(4-Methoxyphenyl)methylene-2-piperidinone (7; R=OMe) was obtained from a reaction of the amine (2; R=OMe) in benzene at 80° for 20 h. Column chromatography on silica (ethyl acetate-dichloromethane, 1:1) gave the lactam (7; R=OMe) (31%) identical to a sample prepared by the aldol/dehydration sequence described below, m.p. 205-207° (Found: C, 72.1; H, 7.1; N, 6.5. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.5%). ν_{max} 3170w, 1660s, 1606m, 1514m, 1488m, 1257s, 1179m, 1027w, 847w cm^{-1}. ^1H n.m.r. δ(200 MHz, d_6-DMSO),1.70, m, 2H, H5; 2.70, m, 2H, H4; 3.21, m, 2H, H6; 3.77, s, 3H, OCH_3; 6.96, d, J 8.8 Hz, 2H and 7.38, d, J 8.8 Hz, 2H, ArH; 7.49, bs, 1H, HC=; 7.73, bs, 1H, NH. ^{13}C n.m.r. δ(50 MHz, d_6-DMSO) 22.84, 26.13 (C4,5); 40.81 (C6); 55.17 (OCH_3); 113.92 (ArCH); 128.05, 128.65 (ArC, C3); 131.33 (ArCH); 133.00 (CH=); 159.04 (ArC); 164.77 (C2). Mass spectrum: m/z 217(M, 46%), 216(100), 174(17), 159(10), 145(10), 115(18).

(E)-3-(4-Cyanophenyl)methylene-2-piperidinone (7; R=CN) was obtained from a reaction of the amine (2; R=CN) in benzene at 90° for 20 h. Column chromatography gave the lactam (7; R=CN) (10%) identical to a sample prepared by the aldol/dehydration sequence, m.p. 197-199°. (Found: C, 73.7; H, 5.5; N, 12.9. $C_{13}H_{12}N_2O$ requires C, 73.6; H, 5.7; N, 13.2%). ν_{max} 2230w, 1662m, 1616m, 1410w, 1337w, 825w cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.90, m, 2H, H5; 2.78, m, 2H, H4; 3.46, m, 2H, H6; 6.78, bs, 1H, NH; 7.46, d, J 8.3 Hz, 2H and 7.68, d, J 8.3 Hz, 2H, ArH; 7.79, bs, 1H, HC=. ^{13}C n.m.r. δ(50 MHz) 22.79, 26.18 (C4,5); 41.92 (C6); 111.36 (ArC); 118.61 (CN); 130.09, 132.01 (ArCH); 132.45 (C3); 133.42 (CH=); 140.37 (ArC); 165.90 (C2). Mass spectrum: m/z 212(M, 25%), 211(100), 184(13), 154(16), 140(20), 127(16).

(E)-3-Phenylmethylene-2-pyrrolidinone (11) and 3-phenyl-(1H)-5,6-dihydropyridin-2-one (12). Reaction of the amine (5) in ethyl acetate at 80 or 90° for 20 h gave the lactams (11) and (12) in ratio *ca.* 3:2 as shown by ^1H n.m.r spectra. Radial chromatography on alumina (ethyl acetate) gave the lactam (12) followed by the lactam (11) (total yield, 80%). (E)-3-Phenylmethylene-2-pyrrolidinone (11) had m.p. 172° (lit.,[7] 172-173°) ^{13}C n.m.r. δ(50 MHz) 26.36 (C4); 39.53 (C5); 128.57, 128.69, 129.59 (ArCH); 129.98 (C3); 130.50 (CH=); 135.65 (ArC); 172.50 (C2).

3-Phenyl-(1H)-5,6-Dihydropyridin-2-one (12), m.p. 158-160° (Found: C, 76.4; H, 6.4; N, 8.1%. $C_{11}H_{11}NO$ requires C, 76.3; H, 6.4; N, 8.1%). ν_{max} 3207w, 1664m, 1616m cm^{-1}. ^1H n.m.r. δ(200 MHz) 2.53, td, J 7.0, 4.5 Hz, 2H, H5; 3.51, td, J 7.0, 2.8 Hz, 2H, H6; 5.93, bs, 1H, NH; 6.75, t, J 4.5 Hz, 1H, H4; 7.29-7.47, m, 5H, ArH. ^{13}C n.m.r. δ(50 MHz) 24.71 (C5); 39.84 (C6); 127.68, 128.01, 128.52 (ArCH); 135.96, 136.52 (C3, ArC); 137.85 (C4); 165.93 (C2). Mass spectrum: m/z 173 (M, 100%), 172(29), 144(93), 117(23), 116(98), 115(78).

(E)-3-(Pent-1-enyl)-2-piperidinone (9; R=Bu) and 3-Pentyl-(1H)-5,6-dihydropyridin-2-one (10; R=Bu). Reaction of non-4-ynylamine (6; R=Bu) in benzene at 90° for 20 h gave a mixture of the lactams (9; R=Bu) and (10; R=Bu) (50%) in ratio *ca.* 3:1 together with recovered amine (6; R=Bu) (50%). The lactams were separated by column chromatography (alumina, ethyl acetate) to give firstly the endocyclic lactam (10; R=Bu) followed by its exocyclic isomer (9; R=Bu).

3-Pentyl-(1H)-5,6-dihydropyridin-2-one (10; R=Bu) (Found: 167.131±0.002. $C_{10}H_{17}NO$ requires 167.1310). ν_{max} 3285w, 1673m, 1624m, 1480w, 1458w cm^{-1}. ^1H n.m.r. δ(200 MHz) 0.84, t, J 6.7 Hz, 3H, CH_3; 1.22-1.44, m, 6H, $CH_3(CH_2)_3$; 2.06-2.32, m, 4H, H5 and CH_2C=; 3.33, td, J 7.1, 2.7 Hz, 2H, H6; 6.29, tt, J 4.3, 1.3 Hz, 1H, H4. ^{13}C n.m.r. δ(50 MHz) 14.06 (CH_3); 22.53, 24.24, 28.19, 30.22, 31.52 ($CH_3(CH_2)_4$, C5); 39.95 (C6); 134.55 (C4); 135.53 (C3); 167.16 (C2). Mass spectrum: m/z 167 (M, 21%), 152(26), 138(100), 125(20), 124(70), 111(31), 110(22), 95(35), 82(42), 81(42), 67(45), 53(40), 41(25).

(E)-3-(Pent-1-enyl)-2-piperidinone (9; R=Bu) b.p. 125°(oven)/0.2 mm. (Found: 167.131±0.002. $C_{10}H_{17}NO$ requires 167.1310). ν_{max} 3202bs, 1674s, 1628s, 1487s, 1466s, 1337s, 1118m cm^{-1}. ^1H n.m.r. δ(200 MHz) 0.90, t, J 7 Hz, 3H, CH_3; 1.25-1.47, m, 4H and 1.83, app. q, J 6 Hz, 2H, H5 and CH_3 $(CH_2)_2$; 2.13, app. q, J 7 Hz, 2H, and 2.44, m, 2H, H4 and CH_2C=; 3.34, m, 2H, H6; 6.83, tt, J 7.5, 1.9 Hz, 1H, HC=; 7.50, bs, 1H, NH. ^{13}C n.m.r. δ(50 MHz) 13.72 (CH_3); 22.27, 22.57, 24.23 ($CH_3(CH_2)_2$, C5); 27.28, 30.51 (CH_2CH=, C4); 41.66 (C6); 128.29 (C3); 138.85 (CH=); 167.05 (C2). Mass spectrum: m/z 167 (M, 51%), 138(100), 125(27), 124(24), 110(23), 99(31), 96(27), 81(32), 79(29), 68(20), 67(59), 53(25), 41(41).

Samples from a reaction in tetrahydrofuran were analysed by ^1H n.m.r. spectroscopy after 20, 48, and 86 h. After 20 h only 5% conversion had occurred with the ratio of (9; R=Bu) : (10; R=Bu) being 20:1. After 48 h the ratio was now 3:1 and after 86 h the ratio was 1:1 with a 20% conversion.

A sample of the pure exocyclic lactam (9; R=Bu) was subjected to the usual rhodium-catalysed reaction conditions at 90° for 20 h. The ^1H n.m.r. spectrum of the product showed that isomerisation had occurred to give a 1:1 mixture of (9; R=Bu) and (10; R=Bu). A similar isomerisation was observed when a solution of (9; R=Bu) (60 mg) in ethanol (10 ml) was refluxed for 4 h with $RhCl_3$ (5 mg) leading to a 1:1 mixture of (9; R=Bu) and (10; R=Bu).

Reaction of pent-4-ynylamine (6; R=H) in benzene at 90° for 20 h resulted in an intractable red-brown residue (*ca.* 30%) and soluble material which was shown to be recovered amine (6; R=H) (*ca.* 50%) with a small amount (*ca.* 5-10%) of *3-methylene-2-piperidinone* (9; R=H) as shown by spectral data.[9] ν_{max} 1673 s cm^{-1}. ^1H n.m.r. δ(300 MHz) 1.87, m, 2H, H5; 2.58, tt, J 5.9, 2.6 Hz, 2H, H4; 3.39, td, J 5.9, 2.6 Hz, 2H, H6; 5.32, m, 1H and 6.22, m 1H (H_2C=). Mass spectrum: m/z 111(M, 100%) 82(61), 67(14).

A reaction in ethyl acetate at 90° for 20 h also gave an intractable residue. Only a trace of 3-methylene-2-piperidinone (9; R=H) was obtained and the major product (*ca.* 25%) was *N-(pent-4-ynyl)acetamide.* ν_{max} 3296 m(br), 2118w, 1652s cm^{-1}. ^1H n.m.r. δ(200 MHz) 1.74, p, J 6.9 Hz, 2H, H2'; 1.99, bs, 4H, CH_3 and H5'; 2.25, td, J 6.9, 2.6 Hz, 2H, H3'; 3.35, td, $J_{1',2'} \approx J_{1',NH}$ 6.7 Hz, 2H, H1'; 6.48, bs, 1H, NH. ^{13}C n.m.r. δ(50 MHz) 15.90 (C2'); 22.97 (CH_3); 27.84 (C3'); 38.59 (C1'); 68.97 (C5'); 83.34 (C4'). Mass spectrum: m/z 124(M-1, 6%), 110(11), 86(12), 83(100), 82(28), 73(38), 72(44).The spectral data was identical to that of an authentic sample of the acetamide.

The aldol/dehydration route to 3-alkylidene and 3-arylidene-2-piperidinones.

N-Boc-2-piperidinone was prepared by the method of Grehn and Ragnarsson,[8] (72%) m.p. 32-33° (lit.,[18] 33-35°).

Conversion to unsaturated lactams (7) and (9).

In a typical reaction sequence N-Boc-2-piperidinone (1.0 g, 5 mmol) in dry THF (10 ml) was added to a solution of LDA (5.5 mmol) in dry THF (30 ml) at -78°. The mixture was stirred for 10 min, allowed to warm to 0°, stirred for a further 30 min and cooled to -78°. Pentanal (0.52 g, 6 mmol) was added *via* a microlitre syringe, the mixture stirred at -78° for 30 min and quenched by the addition of saturated NH_4Cl solution (10 ml). The mixture was allowed to warm to ambient temperature and the product (1.46 g, 100%) isolated in ether. A sample of the product (1.0 g, 3.5 mmol) was dissolved in dry dichloromethane (30 ml) containing triethylamine (1.06 g, 10.5 mmol) and the mixture cooled to -40°. Methanesulfonyl chloride (0.72 g, 6.3 mmol) was added dropwise, the mixture stirred at -40° for 20 min, allowed to warm to ambient temperature and stirred for a further 2 h. A saturated solution of NH_4Cl was added and the crude product (1.32 g) isolated in ether and used directly.

1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) (0.68 ml, 5.5 mmol) was added to a solution of the mesylate (1.0 g, 2.75 mmol) in dry THF (10 ml) and the mixture allowed to stand for 2 h at ambient temperature. The Boc-protected unsaturated lactam, *N-Boc-(E)-3-(pent-1-enyl)-2-piperidinone* was isolated in ether and chromatographed on a column of silica (25 g) (ethyl acetate/light petroleum, 3:1) (0.63 g, 86%). ^{1}H n.m.r. δ(200 MHz) 0.90, t, J 7.0 Hz, 3H, CH_3; 1.30-1.52, m, 4H, $CH_2CH_2CH_3$; 1.54, s, 9H, Boc-CH_3; 1.86, m, 2H, H5; 2.13, m, 2H and 2.46,m, 2H, H4 and CH_2CH=; 6.97, tt, J 7.5, 2.1 Hz, 1H, HC=. ^{13}C n.m.r. δ(50 MHz) 13.08 (CH_3); 21.55, 21.61, 23.57 (C5, $CH_2CH_2CH_3$); 27.20 (Boc-CH_3); 27.26, 29.77 (C4, CH_2CH=); 45.09 (C6); 81.52 (Boc-CCH_3); 129.15 (C3); 141.76 (CH=); 152.30 (Boc-CO); 164.37 (C2).

Deprotection of a sample of the Boc-protected lactam (120 mg) in dichloromethane (2 ml) involved addition of trifluoroacetic acid (0.15 ml) and reaction for 2 h at ambient temperature. Dichloromethane was removed by distillation and the product taken up in ether. The ether solution was washed ($NaHCO_3$), dried (Na_2SO_4) and the ether removed to give (9) as a colourless oil (70 mg, 93%). Overall yield from the Boc-protected-2-piperidinone was 80%.

The same procedure was used to prepare the arylidene lactams (7; R=CN and OMe) using 4-cyano and 4-methoxybenzaldehydes, overall yields 34 and 63% respectively. Spectral data for the intermediate Boc-protected lactams are summarised:-

N-Boc-(E)-3-(4-methoxylphenylmethylene)-2-piperidinone. ^{1}H n.m.r. δ(200 MHz) 1.56, s, 9H, Boc-CH_3; 1.88, m, 2H, H5; 2.79, m, 2H, H4; 3.74, m, 2H, H6; 3.83, s, 3H, OCH_3; 6.91, d, J 8.8 Hz, 2H and 7.37, d, J 8.8 Hz, 2H, ArH; 7.82, bs, 1H, HC=. ^{13}C n.m.r. δ(50 MHz) 22.48, 26.29 (C4,5); 27.94 (Boc-CH_3); 45.70 (C6); 55.16 (OCH_3); 82.63 (Boc-C-CH_3); 113.75 (ArCH); 128.15, 128.33 (ArC, C3): 131.72 (ArCH); 138.16 (CH=); 153.06 (Boc-CO); 159.75 (ArC); 165.85 (C2).

N-Boc-(E)-3-(4-cyanophenylmethylene)-2-piperidinone. ^{1}H n.m.r. δ(200 MHz) 1.57, s, 9H, Boc-CH_3; 1.91, m, 2H, H5; 2.76, m, 2H, H4; 3.75, m, 2H, H6; 7.47, d, J 8.2 Hz, 2H and 7.69, d, J 8.2 Hz, 2H, ArH; 7.84, bs, 1H, HC=. ^{13}C n.m.r. δ(50 MHz) 20.02, 25.91 (C4,5); 27.66 (Boc-CH_3); 45.64 (C6); 82.78 (Boc-C-CH_3); 111.36 (ArC); 118.18 (CN); 129.96, 131.77 (ArCH); 133.50 (C3); 135.60 (CH=), 139.82 (ArC); 152.37 (Boc-CO); 164.48 (C2).

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