Co-cyclizations of nitrogen-containing acetylenes induced by a nickel triphenylphosphine complex to give aminoindane, isoindoline and isoindolinone derivatives

D. Malcolm Duckworth,[a] Simon Lee-Wong,[b] Alexandra M. Z. Slawin,[b] Edward H. Smith*,[b] and David J. Williams[b]

[a] *SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Ave., Harlow, Essex CM19 5AW, UK*

[b] *Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, UK*

***N*-Methyl-, *N*,*N*-dimethyl-, *N*,*N*-diethylprop-2-ynylamines, *N*-prop-2-ynylacetamide and *N*-prop-2-ynylbenzamide are co-cyclized with diethyl hepta-1,6-diyne-4,4-dicarboxylate at room temperature in the presence of stoichiometric nickel(0) to give amino- and amido-indanes in fair to good yields. The structure of the product from *N*-prop-2-ynylbenzamide was established by X-ray crystallography. Likewise, *N*-alkyldiprop-2-ynylamines co-cyclize with methyl prop-2-ynyl ether to give isoindolines albeit in lower yields; the corresponding reaction of short chain *N*-alkynylalkynamides requires heating to 60 °C but gives isoindolinones and a 1,4-dihydroisoquinolin-3(2*H*)-one as mixtures of regioisomers in good yields. Attempts to synthesize medium-ring, benzo-fused lactams by this method failed.**

The ability of nickel in its zero valent oxidation state to catalyse or mediate the co-cyclization of α,ω-diynes and monoynes to give bicyclic aromatics has been amply demonstrated with a number of alkynes bearing alkyl groups or oxygen-containing substituents such as alcohol, ether, ketone and ester.[1] There is a dearth of reports, however, concerning this reaction and nitrogen-containing alkynes. Thus, Chiusoli, Pallini and Terenghi reported in 1983 that a prop-2-ynylamine and two diprop-2-ynylamines which were sterically hindered about the nitrogen atoms co-cyclized to isoindoline derivatives,[2] we showed that a diyneamide and a monoyneimide both successfully underwent the reaction[1c] and, most recently, Sato, Nishimata and Mori prepared isoindoline and tetrahydroisoquinoline derivatives from diynetosylamides and triyneamines.[3] A wider investigation of alkynylamines and alkynylamides in these co-cyclizations has not been made previously, however, and forms the basis of the present report.[4]

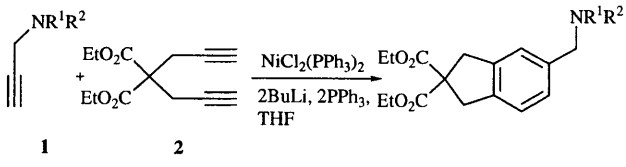
Results and discussion

Co-cyclization of prop-2-ynylamine derivatives with a non-nitrogeneous diyne

In a previous publication it had been shown that the parent prop-2-ynylamine failed to co-cyclize with dimethyl deca-2,8-diynedioate.[1c] This was thought to be due to an interaction of the nickel with the NH bonds of the unhindered, primary amine as had been suggested by Chiusoli, Pallini and Terenghi.[2] Thus, our first experiments were with the tertiary congeners **1a**,**b** which do not contain such bonds. These reacted well under the standard conditions [*i.e.* in the presence of stoichiometric tetrakis(triphenylphosphine)nickel(0) in dry THF at room temperature overnight] with diethyl hepta-1,6-diyne-4,4-dicarboxylate **2** (Scheme 1). The yields of indanes **3a** and **3b** were comparable indicating that steric hindrance about the nitrogen atom did not inhibit the reaction to any great extent, in agreement with the findings of the Italian workers.

However, secondary prop-2-ynylamine **1c** also successfully cyclized with **2** to give the aminoindane **3c** in good yield. The result from this reaction showed that the presence of one NH in the amine was not deleterious to co-cyclization. We were not so confident that this would be true with amides which bear a significantly more acidic NH than that of amines, especially since nona-2,8-diynoic acid amide had previously proved a poor substrate (in terms of yield) for co-cyclization.[1c] In the event, both *N*-prop-2-ynylacetamide **1d** and *N*-prop-2-ynylbenzamide **1e** gave amidoindanes in yields (40 and 42% respectively) lower than for the amines. A single crystal X-ray analysis of **3e** established its structure (Fig. 1). This provided the first such determination of an indane prepared by this reaction and set the structural assignments of analogues in this and previous papers on a solid footing.

Having established that a monoyne may bear either an amine or an amide functionality without serious detriment to the



1 **2**

3a $R^1 = R^2 = Et$ (60%)
b $R^1 = R^2 = Me$ (62%)
c $R^1 = H, R^2 = Me$ (72%)
d $R^1 = H, R^2 = MeCO$ (40%)
e $R^1 = H, R^2 = PhCO$ (42%)

Scheme 1

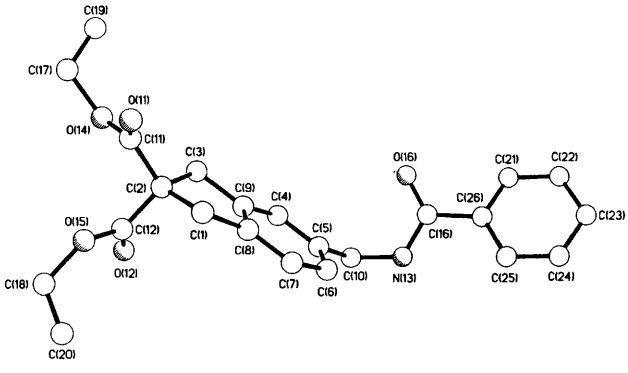
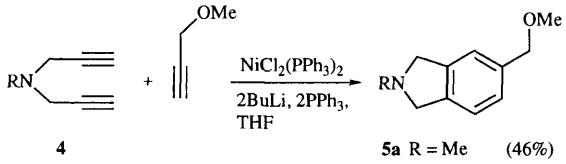


Fig. 1

co-cyclization, we turned our attention to diynes bearing these moieties.

Co-cyclization of diyneamines and diyneamides with methyl prop-2-ynyl ether

The diprop-2-ynylamines **4a–c** were treated with methyl prop-2-ynyl ether under standard conditions to give the isoindolines **5a–c** albeit in low yields (Scheme 2). The corresponding amide

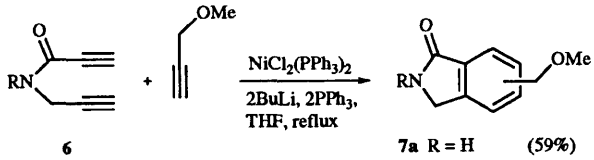


4

5a R = Me (46%)
b R = $PhCH_2$ (36%)
c R = Ph_2CH (10%)

Scheme 2

6a reacted under these conditions but did not produce any identifiable product. However, an increase in the reaction temperature to 60 °C effected the desired co-cyclization. The product isoindolinone **7a** was isolated as a 1:1 mixture of regioisomers inseparable by column chromatography; the same conditions led to the congeners **7b–d** likewise as a mixture of regioisomers in approximately equal amounts (Scheme 3). The



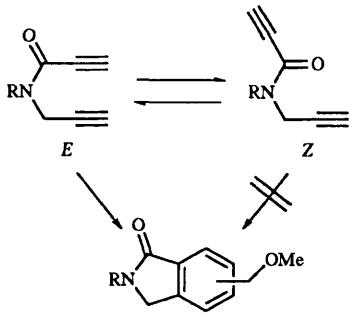
6

7a R = H (59%)
b R = Me (34%)
c R = $PhCH_2$ (4%)
d R = Ph_2CH (63%)

Scheme 3

low yield of the *N*-benzyl congener mixture **7c** is a consequence of the tenacity with which it occluded triphenylphosphine oxide (a by-product of the work-up of these reactions) which forced extensive chromatography in order to obtain a pure sample; a yield in excess of 50% was indicated by the integration of the ^1H NMR spectrum of the crude product.

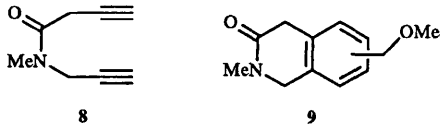
The amides **6b–d** each existed as two rotamers in approximately 1:1 ratio in agreement with known *N*,*N*-dialkylamides.[5] One rotamer predominates for the secondary amide **6a** (ratio 16:1) and by analogy with known secondary alkylamides it is assigned the extended *Z*-configuration.[6] This rotamer is clearly not capable of interaction of the two alkyne groups with the same nickel and presumably *Z*–*E* conversion must occur before reaction with the nickel proceeds to give the isoindolinone (Scheme 4), an isomerization which requires



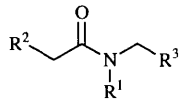
Scheme 4

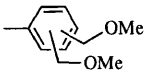
heat.[6] This explanation is supported by the result of a variable temperature ^1H NMR study of **6a**; the peaks for the alkynic protons of the CH_2CCH and COCCH groups and the methylene protons of the former (at δ_H 2.3, 3.2 and 4.2 respectively) in the minor rotamer all show significant broadening at 60 °C (the corresponding peaks of the major rotamer, being closer to the weighted average, do not show this as clearly). For the tertiary amides the more favourable *E*-rotamer present presumably has not got an ideal bite angle for intramolecular co-ordination of both alkynes with nickel(0) and hence again heat is required.

The method was extended to the synthesis from amide **8** of the rather rare 1,4-dihydroisoquinolin-3(2*H*)-one **9**[7] in 59% yield; the ^1H NMR spectrum of this product suggested only one isomer but this was clearly discounted by inspection of the ^{13}C NMR spectrum which showed doubling of a number of the peaks expected. Attempts to extend the reaction to the synthesis of corresponding polyhydro-benzazepinones, -benzazocinones and -benzazoninones from amides **10**, **11** and **12**, **13**, **14** and **15**, respectively, failed. Although amides **10–15** all reacted, the only identifiable product (7%) from these attempts was compound **16** (as a mixture of two regioisomers) derived from the reaction of two monoyne units and the *N*-terminal alkyne group of the diyne **10**.



8 **9**



10 R^1 = H, R^2 = $CH_2C{\equiv}CH$, R^3 = $C{\equiv}CH$
11 R^1 = Me, R^2 = $CH_2C{\equiv}CH$, R^3 = $C{\equiv}CH$
12 R^1 = H, R^2 = R^3 = $CH_2C{\equiv}CH$
13 R^1 = H, R^2 = $(CH_2)_2C{\equiv}CH$, R^3 = $C{\equiv}CH$
14 R^1 = Me, R^2 = $(CH_2)_2C{\equiv}CH$, R^3 = $C{\equiv}CH$
15 R^1 = H, R^2 = $(CH_2)_2C{\equiv}CH$, R^3 = $CH_2C{\equiv}CH$
16 R^1 = H, R^2 = $CH_2C{\equiv}CH$, R^3 = 

Conclusions

Whilst yields are more variable than for non-nitrogeneous alkynes, it may be concluded that secondary and tertiary amino groups and tertiary amides are tolerated in these nickel(0) promoted co-cyclizations whether they are in the monoyne or diyne unit. Amides in the diyne require heating possibly because of unfavourable configurations which place the alkynic units further apart than required for co-cyclization. Secondary amides are more capricious than the tertiary congeners.

An entropic disadvantage, in addition to the configurational problems mentioned above, seems to outweigh any possible templating upon nickel [1b] which might otherwise favour the co-cyclization of medium length diynes with methyl prop-2-ynyl ether to medium ring lactams. In these cases the rate of reaction of one alkyne unit of the diyne with two equivalents of monoyne appears to be more rapid than the combined rates of configurational CON isomerism and chelation of the diyne.

Experimental

Melting points were determined on a Kofler hot stage or Gallenkamp apparatus and are uncorrected. IR Spectra were recorded on a Perkin-Elmer 881 grating spectrophotometer as thin films or Nujol mulls unless otherwise stated. ^1H and ^{13}C NMR Spectra were recorded on JEOL FX 90Q, Bruker WM-250, JEOL GSQ 270, Bruker AMX-400 and Bruker AM-500 spectrometers in $CDCl_3$ with tetramethylsilane or residual

chloroform as internal standards; signals are quoted as singlet (s), doublet (d), double doublet (dd), triplet (t), multiplet (m) and broad (br) and J values are given in Hz. Mass spectra were recorded on a VG Micromass 7070B machine by the EI method unless otherwise indicated.

Preparative gravity column chromatography was performed on Crosfield Sorbsil C60 silica gel. Petroleum refers to light petroleum of bp 40–60 °C. Ether refers to diethyl ether. Ether and THF (tetrahydrofuran) were distilled from sodium–benzophenone and potassium metal respectively under argon just prior to use. Dichloromethane was distilled from phosphorus pentoxide. Butyllithium and *N*-methylprop-2-ynylamine were purchased from Aldrich Chemicals. *N*,*N*-Dimethyl- and *N*,*N*-diethyl-prop-2-ynylamine,[8] *N*-prop-2-ynylacetamide,[9] *N*-prop-2-ynylbenzamide,[10] *N*-prop-2-ynylbenzylamine,[11] *N*-methyldiprop-2-ynylamine[12] and *N*-benzyldiprop-2-ynylamine[13] were prepared according to the literature. All other solvents and reagents were purified by standard methods.

General procedure for the co-cyclization of diethyl hepta-1,6-diyne-4,4-dicarboxylate with monoynes to give the amino indanes 3

The co-cyclizations were carried out according to the literature procedure.[1c] The reactions were then worked up as indicated for each compound below.

Diethyl 5-(*N*,*N*-diethylaminomethyl)indane-2,2-dicarboxylate 3a. From diethyl hepta-1,6-diyne-4,4-dicarboxylate (179 mg, 0.76 mmol) and *N*,*N*-diethylprop-2-ynylamine (337 mg, 3.04 mmol). The reaction was quenched with aq. HCl (5 mol dm^{-3}; 10 cm^3) and exposed to air. The mixture was evaporated on a rotary evaporator and the residue was diluted with water (50 cm^3). The aqueous layer was extracted with ether (4 × 20 cm^3) to remove non-basic organic material. The aqueous layer was then basified carefully with solid sodium hydrogen carbonate to pH 8 and extracted with ethyl acetate (4 × 20 cm^3). The combined extracts were dried ($MgSO_4$), filtered and concentrated to give the product which was chromatographed using methanol–ethyl acetate (1:20) as eluent. The pure indane was obtained as a light-brown oil (160 mg, 60%) (Found: C, 68.8; H, 8.8; N, 3.3%; M^+, 347.2099. $C_{20}H_{29}NO_4$ requires C, 69.14; H, 8.41; N, 4.03%; M, 347.2097); ν_{max}/cm^{-1} 1731 (CO); δ_H(270 MHz) 1.0 (6 H, t, J 6, 2 × CH_2Me), 1.25 (6 H, t, J 6, 2 × CH_2Me), 2.5 (4 H, q, J 6, 2 × $MeCH_2N$), 3.5 (2 H, s, $ArCH_2N$), 3.6 (4 H, s, 2 × ring CH_2), 4.2 (4 H, q, J 6, 2 × CH_2O), 7.1 (2 H, apparent s, ArH) and 7.15 (1 H, apparent s, ArH); δ_C(67.5 MHz) 12 (Me), 14 (Me), 40.2 (ring CH_2), 40.4 (ring CH_2), 47 (CH_2), 57 (CH_2), 60 (ring C), 62 (CH_2), 124, 125, 128, 138, 139, 140 and 172 (CO); m/z 347 (M^+, 22%), 332 (M^+ − Me, 44%), 275 (M^+ − Et_2N, 50%) and 201 (100%).

Diethyl 5-(*N*,*N*-dimethylaminomethyl)indane-2,2-dicarboxylate 3b. From diethyl hepta-1,6-diyne-4,4-dicarboxylate (207 mg, 0.88 mmol) and *N*,*N*-dimethylprop-2-ynylamine (220 mg, 2.66 mmol). The reaction was worked up as above to give the product after column chromatography [methanol–ethyl acetate (1:20)] as an oil (176 mg, 62%) (Found: C, 67.6; H, 8.1; N, 4.3%; M^+, 319.1786. $C_{18}H_{25}NO_4$ requires C, 67.69; H, 7.89; N, 4.39%; M^+, 319.1784); ν_{max}/cm^{-1} 1746 (CO); δ_H(90 MHz) 1.4 (6 H, t, J 7, 2 × CH_2Me), 2.4 (6 H, s, NMe_2), 3.55 (2 H, s, CH_2N), 3.75 (4 H, s, 2 × ring CH_2), 4.25 (4 H, q, J 7, 2 × CH_2O) and 7.25 (3 H, m, ArH); δ_C(67.5 MHz) 14 (Me), 40.1 (CH_2), 40.2 (CH_2), 45 (CH_2), 60 (ring C), 62 (NMe_2), 64 (CH_2), 124, 125, 128, 137, 139, 140 and 172 (CO); m/z 319 (M^+, 60%), 275 (M^+ − NMe_2, 2.5%), 201 (25%), 129 (28%) and 58 ($Me_2NCH_2^+$, 100%).

Diethyl 5-(*N*-methylaminomethyl)indane-2,2-dicarboxylate 3c. From diethyl hepta-1,6-diyne-4,4-dicarboxylate (213 mg, 0.90 mmol) and *N*-methylprop-2-ynylamine (256 mg, 3.60 mmol). The reaction was worked up as above to give the product after column chromatography [methanol–ether (1:4)] as an oil (197 mg, 72%) (Found: MH^+, 306.1705. $C_{17}H_{24}NO_4$ requires M, 306.1705); ν_{max}/cm^{-1} 1730 (CO); δ_H(270 MHz) 1.25 (6 H, t, J 7.5, 2 × Me), 2.1 (1 H, br s, NH), 2.45 (3 H, s, NMe), 3.55 (4 H, s, 2 × ring CH_2), 3.7 (2 H, s, CH_2N), 4.2 (4 H, q, J 7.5, 2 × CH_2OCO) and 7.1–7.2 (3 H, m, ArH); δ_C(67.5 MHz) 14 (2 × Me), 40.2 (CH_2), 40.3 (CH_2), 54 (CH_2), 60 (ring C), 62 (2 × CH_2O), 124, 124.5, 125, 128, 140, 141 and 172 (CO); m/z 306 (MH^+, 100%).

Diethyl 5-(*N*-acetylaminomethyl)indane-2,2-dicarboxylate 3d. From diethyl hepta-1,6-diyne-4,4-dicarboxylate (213 mg, 0.90 mmol) and *N*-prop-2-ynylacetamide (349 mg, 3.60 mmol). The reaction was worked up as above to give the product after column chromatography [light petroleum–ether (1:1)] as an oil (120 mg, 40%) (Found: M^+, 333.1557. $C_{18}H_{23}NO_5$ requires M, 333.1576); ν_{max}/cm^{-1} 3278 (NH), 1726 (ester CO) and 1670 (amide CO); δ_H(270 MHz) 1.2 (6 H, t, J 7, 2 × Me), 1.9 (3 H, s, COMe), 3.5 (4 H, 2 × s, 2 × ring CH_2), 4.15 (4 H, q, J 7, 2 × CH_2OCO), 4.25 (2 H, d, J 5, CH_2N), 6.6 (1 H, br s, NH) and 7.0–7.1 (3 H, m, ArH); m/z (CI) 351 (MNH_4^+, 18%), 334 (MH^+, 6) and 279 (100).

Diethyl 5-(*N*-benzoylaminomethyl)indane-2,2-dicarboxylate 3e. From diethyl hepta-1,6-diyne-4,4-dicarboxylate (213 mg, 0.90 mmol) and *N*-prop-2-ynylbenzamide (572 mg, 3.60 mmol). The reaction was worked up as above to give the product after column chromatography as a white solid, mp 98.0–99.0 °C (149 mg, 42%) (Found: C, 69.7; H, 6.4; N, 3.4. $C_{23}H_{25}NO_5$ requires C, 69.86; H, 6.37; N, 3.54%); ν_{max}/cm^{-1} 3344 (NH), 1731 (ester CO) and 1637 (amide CO); δ_H(270 MHz) 1.25 (6 H, t, J 7, 2 × CH_2Me), 3.6 (4 H, s, 2 × ring CH_2), 4.2 (4 H, q, J 7, 2 × CH_2O), 4.6 (2 H, d, J 5, CH_2N), 6.4 (1 H, br s, NH), 7.2 (3 H, m, indane ArH), 7.45 (3 H, m, *m*- and *p*-benzoyl ArH) and 7.8 (2 H, d, J 9, *o*-benzoyl ArH); δ_C(67.5 MHz) 14 (Me), 40.2 (CH_2), 40.3 (CH_2), 44 (CH_2), 60 (ring C), 62 (CH_2), 124, 124.5, 127, 127, 128.5, 131.5, 134, 137, 139.5, 141, 167 (amide CO) and 172 (ester CO).

(Diphenylmethyl)diprop-2-ynylamine 4c and (diphenylmethyl)-prop-2-ynylamine

Diphenylmethylamine (1.83 g, 10 mmol), prop-2-ynyl bromide (80% solution in toluene, 4.46 g, 30 mmol) and potassium carbonate (6.91 g, 50 mmol) were heated to reflux in acetonitrile (40 cm^3) for 24 h. The mixture was cooled to room temperature and evaporated on a rotary evaporator. Water (30 cm^3) was added to the residue. The mixture was extracted with ether (3 × 30 cm^3) and the combined extracts were dried (Na_2SO_4), filtered and concentrated to give a white solid. This was column chromatographed using light petroleum–ether (10:1) as eluent to give the product **4c** as a white solid, mp 85–86 °C (2.25 g, 87%) (Found: C, 87.8; H, 6.7; N, 5.3. $C_{19}H_{17}N$ requires C, 87.99; H, 6.61; N, 5.40%); ν_{max}/cm^{-1} 3286 (CCH); δ_H(270 MHz) 2.35 (2 H, t, J 2, 2 × CCH), 3.6 (4 H, d, J 2, 2 × CH_2), 4.75 (1 H, s, CHN), 7.3 (6 H, m, *m*- and *p*-ArH) and 7.55 (4 H, d, J 8, *o*-ArH); δ_C(67.5 MHz) 40 (CH_2), 71 (CH), 73 (CCH), 79 (CCH), 127, 128, 129 and 142. A solution of diphenylmethylamine (4 g, 21.8 mmol) and prop-2-ynyl bromide (80% solution in toluene, 1.62 g, 10.9 mmol) in ether (80 cm^3) was heated at reflux for 10 h. The mixture was cooled to room temperature and washed with water (3 × 20 cm^3). The ethereal solution was dried, filtered and rotary evaporated to give an oil which was chromatographed using light petroleum–ether (1:1) as eluent. (Diphenylmethyl)prop-2-ynylamine was obtained as a pale yellow solid (1.63 g, 68%); mp 60–61 °C (Found: C, 86.0; H, 6.7; N, 6.1%; M^+, 221.1196. $C_{16}H_{15}N$ requires C, 86.84; H, 6.83; N, 6.33%; M, 221.1204); ν_{max}/cm^{-1} 3270 (NH + CCH); δ_H(90 MHz) 1.8 (1 H, br s, NH), 2.25 (1 H, t, J 2, CCH), 3.4 (2 H, d, J 2, CH_2), 5.15 (1 H, s, CH) and 7.2–7.6 (10 H, m, ArH); m/z 221 (M^+, 100%) and 167 (Ph_2CH^+, 18%). Earlier fractions gave (diphenylmethyl)diprop-2-ynylamine (303 mg).

5-Methoxymethyl-*N*-methylisoindoline 5a

N-Methyldiprop-2-ynylamine (41 mg, 0.38 mmol) in dry THF (10 cm^3) was added to a solution of the nickel(0) reagent (1 equiv.) prepared according to the literature procedure.[1c] After 10 min at room temperature methyl prop-2-ynyl ether (107 mg, 1.53 mmol) was added, the mixture was stirred at room temperature for 24 h and then quenched with aq. HCl (5 mol dm^{-3}; 10 cm^3). The mixture was evaporated on a rotary evaporator and the residual aqueous solution was diluted with water (20 cm^3) and washed with ether (2 × 15 cm^3). The aqueous solution was then basified with sodium hydrogen carbonate and extracted with ether (3 × 20 cm^3). The combined ether extracts were dried and concentrated to a brown oil which was chromatographed using methanol–ether (1:4) as eluent. The isoindoline was obtained as a yellow oil (31 mg, 46%) (Found: MH^+, 178.1236. $C_{11}H_{16}NO$ requires *M*, 178.1232); ν_{max}/cm^{-1} 1695 and 1096; δ_H(270 MHz) 2.6 (3 H, s, NMe), 3.35 (3 H, s, OMe), 3.9 (4 H, s, 2 × CH_2N), 4.4 (2 H, s, CH_2O), 7.10 (1 H, s, 4-ArH) and 7.15 (2 H, d, *J* 9, 6,7-ArH); δ_C(125 MHz) 42 (NMe), 58 (OMe), 60.8 (CH_2N), 60.9 (CH_2N), 75 (CH_2O), 121.8, 122, 126.5, 137, 140 and 141; *m*/*z* 178 (MH^+, 100%) and 144 (17).

***N*-Benzyl-5-methoxymethylisoindoline 5b**

Prepared according to the same procedure used for **5a** using *N*-benzyldiprop-2-ynylamine (165 mg, 0.90 mmol), nickel(0) reagent (1 equiv.) and methyl prop-2-ynyl ether (4 equiv.) in dry THF (25 cm^3). The product was extracted from the basic solution with ethyl acetate (3 × 20 cm^3) as a brown oil which was chromatographed using methanol–ether (1:20) as eluent. The isoindoline was obtained as a yellow oil (82 mg, 36%) (Found: MH^+, 254.1537. $C_{17}H_{20}NO$ requires *M*, 254.1545); ν_{max}/cm^{-1} 1660, 1559, 1096 and 707; δ_H(270 MHz) 3.4 (3 H, s, OMe), 3.95 (6 H, 2 × s, 3 × NCH_2), 4.4 (2 H, s, CH_2O), 7.10 (1 H, s, 4-ArH), 7.15 (2 H, d, *J* 9, 6,7-ArH) and 7.25–7.5 (5 H, m, Ph); δ_C(125 MHz) 58 (MeO), 58.7 (CH_2N), 58.8 (CH_2N), 60 (CH_2N), 75 (CH_2O), 121.8, 122, 126, 127, 128.3, 128.7, 137, 139, 140 and 140.5; *m*/*z* 254 (MH^+, 100%), 162 (M − $PhCH_2$, 22) and 91 ($PhCH_2^+$, 18).

***N*-(Diphenylmethyl)-5-methoxymethylisoindoline 5c.** Prepared according to the same procedure used for **5a** using (diphenylmethyl)diprop-2-ynylamine (82 mg, 0.31 mmol), nickel(0) reagent (1 equiv.) and methyl prop-2-ynyl ether (4 equiv.) in dry THF (10 cm^3). The reaction was quenched with saturated aqueous ammonium chloride (10 cm^3). After work-up as for **5a** the product was extracted from the basic solution with ethyl acetate (3 × 20 cm^3) as a brown oil which was chromatographed using light petroleum–ether (2:1) as eluent. The isoindoline was obtained as a yellow oil (10 mg, 10%) (Found: MH^+, 330.1873. $C_{23}H_{24}NO$ requires *M*, 330.1858); δ_H(270 MHz) 3.4 (3 H, s, OMe), 3.85 (4 H, s, 2 × CH_2N), 4.45 (2 H, s, CH_2O), 4.7 (1 H, s, CHN) and 7.1–7.6 (13 H, m, ArH); δ_C(125 MHz) 58 (OMe), 58.5 (CH_2N), 58.6 (CH_2N), 75 (CH_2O), 76 (CHN), 121.8, 122, 126.5, 127, 127.5, 128, 129, 130, 137, 139.5, 140 and 144.

General procedure for the preparation of *N*-alkynylalkynamides 6a–d, 8, 10, 11, 12, 13, 14

A stirred solution of alkynoic acid (0.3 mol dm^{-3}) in dry ether was cooled in ice and treated with dicyclohexylcarbodiimide (DCC) (1.1 equiv.). After 5 min a solution of the alkynylamine (1 equiv., 0.6 mol dm^{-3}) in ether was added dropwise to the reaction mixture and stirring was continued for the appropriate time. The mixture was then filtered through Celite, the latter was washed with dichloromethane (2 × 10 cm^3) and the filtrate and washings were combined and rotary evaporated to give the crude amide. This was chromatographed with the appropriate eluent.

***N*-Prop-2-ynylpropynamide 6a.** From propynoic acid (200 mg, 2.86 mmol), DCC (649 mg, 3.15 mmol) and prop-2-ynylamine (158 mg, 2.86 mmol) in ether (15 cm^3); the mixture was stirred for 90 min at 0 °C. Chromatography using ether as eluent gave the amide as an orange oil (200 mg, 65%); ν_{max}/cm^{-1} 3290 (NH + 2 × CH), 2114 (CC), 1634 (CONH) and 1535 (CONH); δ_H(90 MHz) major rotamer: 2.2 (1 H, t, *J* 2.6, CCH), 2.85 (1 H, s, COCCH), 4.0 (2 H, dd, *J* 2.6, 5, CH_2N) and 7.0 (1 H, br s, NH); minor rotamer: 2.3 (1 H, t, *J* 2.6, CCH), 3.25 (1 H, s, COCCH), 4.2 (2 H, dd, *J* 2.6, 5, CH_2N) and 6.5 (1 H, br s, NH); δ_C(67.5 MHz) 33 (CH_2N), 72 (*C*CH), 74.5 (C*C*H), 76.5 (*C*CH), 78 (*C*CH) and 152 (CO); *m*/*z* 108 (MH^+, 100%).

***N*-Methyl-*N*-prop-2-ynylpropynamide 6b.** From propynoic acid (300 mg, 4.28 mmol), DCC (972 mg, 4.71 mmol) and *N*-methylprop-2-ynylamine (296 mg, 4.28 mmol) in ether (20 cm^3); the mixture was stirred for 90 min at 0 °C. Chromatography using ether as eluent gave the amide (two rotamers in a 6:7 ratio) as a pale yellow oil (291 mg, 56%); ν_{max}/cm^{-1} 3282 (CH), 2108 (CC) and 1633 (CON); δ_H(270 MHz) 2.2 (1 H, t, *J* 3, CCH, major rotamer), 2.30 (1 H, t, *J* 3, CCH, minor rotamer), 2.95 (3 H, s, NMe, minor rotamer), 3.15 (1 H, s, COCCH, major rotamer), 3.16 (1 H, s, COCCH, minor rotamer), 3.20 (3 H, s, NMe, major rotamer), 4.15 (2 H, d, *J* 3, CH_2N, major rotamer) and 4.35 (2 H, d, *J* 3, CH_2N, minor rotamer); δ_C(125 MHz) 31.5 (CH_2N, minor rotamer), 35 (NMe, major rotamer), 35.3 (CH_2N, major rotamer), 40 (NMe, minor rotamer), 72.5 (*C*CH, major rotamer), 73 (*C*CH, minor rotamer), 74.8 (*C*CH, minor rotamer), 75 (*C*CH, major rotamer), 79.6 (*C*CH, minor rotamer), 79.7 (*C*CH, major rotamer), 152.7 (CO, minor rotamer) and 152.9 (CO, major rotamer); *m*/*z* 121 (M^+, 48%), 68 (M^+ − COCCH, 63) and 66 (100).

***N*-Benzyl-*N*-prop-2-ynylpropynamide 6c.** From propynoic acid (196 mg, 2.80 mmol), DCC (635 mg, 3.08 mmol) and *N*-benzylprop-2-ynylamine (410 mg, 2.80 mmol) in ether (15 cm^3); the mixture was stirred for 2 h at 0 °C and then a further 20 h at room temperature. Chromatography using light petroleum–ether (1:1) as eluent gave the amide (two rotamers in a 2:3 ratio) as a pale yellow oil (220 mg, 40%) (Found: C, 78.9; H, 5.6; N, 6.6. $C_{13}H_{11}NO$ requires C, 79.17; H, 5.62; N, 7.10%); ν_{max}/cm^{-1} 3287 (CH), 2106 (CC) and 1650 (CON); δ_H(270 MHz) 2.2 (1 H, t, *J* 3, CCH, major rotamer), 2.35 (1 H, t, *J* 3, CCH, minor rotamer), 3.19 (1 H, s, COCCH, major rotamer), 3.20 (1 H, s, COCCH, minor rotamer), 4.10 (2 H, d, *J* 3, CH_2N, major rotamer), 4.25 (2 H, d, *J* 3, CH_2N, minor rotamer), 4.75 (2 H, s, $PhCH_2N$, minor rotamer), 4.95 (2 H, s, $PhCH_2N$, major rotamer) and 7.2–7.4 (5 H, m, Ph, both rotamers); δ_C(125 MHz) 32 (CH_2N, major rotamer), 37 (CH_2N, minor rotamer), 46 ($PhCH_2N$, minor rotamer), 51 ($PhCH_2N$, major rotamer), 72.5 (*C*CH, major rotamer), 73 (*C*CH, minor rotamer), 75 (*C*CH, minor rotamer), 75.4 (*C*CH, major rotamer), 77.3 (*C*CH, major and minor rotamers), 79.7 (*C*CH, major rotamer), 79.8 (*C*CH, minor rotamer), 127.7, 127.9, 128, 128.5, 128.7, 128.9, 135, 135.3, 152.9 (CO, major rotamer) and 153 (CO, minor rotamer); *m*/*z* 197 (M^+, 90%), 158 (M^+ − CH_2CCH, 100) and 91 ($PhCH_2^+$, 72).

***N*-Diphenylmethyl-*N*-prop-2-ynylpropynamide 6d.** From propynoic acid (336 mg, 4.79 mmol), DCC (1.09 g, 5.27 mmol) and *N*-(diphenylmethyl)prop-2-ynylamine (1.06 g, 4.79 mmol) in ether (25 cm^3); the mixture was stirred for 3 h at 0 °C and then a further 16 h at room temperature. Chromatography using light petroleum–ether (1:1) as eluent gave the amide (two rotamers in a 2:3 ratio) as a pale yellow oil (662 mg, 51%) (Found: C, 83.5; H, 5.1. $C_{19}H_{15}NO$ requires C, 83.49; H, 5.53%); ν_{max}/cm^{-1} 3288 (CH), 2109 (CC) and 1650 (CON); δ_H(270 MHz) 1.9 (1 H, t, *J* 3, CCH, major rotamer), 2.05 (1 H, t, *J* 3, CCH, minor rotamer), 3.15 (1 H, s, COCCH, major rotamer), 3.20 (1 H, s, COCCH, minor rotamer), 4.0 (2 H, d, *J* 3, CH_2N, major rotamer), 4.25 (2 H, d, *J* 3, CH_2N, minor rotamer), 6.9 (1 H, s, CHN, minor rotamer), 6.95 (1 H, s, CHN, major rotamer) and 7.2–7.45 (10 H, m, 2 × Ph, both rotamers); δ_C(125 MHz) 33 (CH_2N, major rotamer), 36 (CH_2N, minor rotamer), 62 (CHN, minor rotamer), 66 (CHN, major rotamer), 71 (*C*CH, major

rotamer), 72 (CCH, minor rotamer), 75.3 (CCH, minor rotamer), 75.5 (CCH, major rotamer), 78 (CCH, major rotamer), 78.5 (CCH, minor rotamer), 79.8 (CCH, minor rotamer), 80 (CCH, major rotamer), 127.7, 128, 128.3, 128.5, 128.5, 128.8, 137 and 154 (CO, both rotamers); *m/z* 274 (MH^+, 78%) and 167 (Ph_2CH^+, 100).

***N*-Methyl-*N*-prop-2-ynylbut-3-ynamide 8.** From but-3-ynoic acid (364 mg, 4.33 mmol), DCC (1.07 g, 5.2 mmol) and *N*-methylprop-2-ynylamine (359 mg, 5.2 mmol) in dichloromethane (25 cm^3); the mixture was stirred for 24 h at room temperature. Chromatography using light petroleum–ether (1:2) as eluent gave the amide (two rotamers in a 2:1 ratio) as a pale yellow oil (236 mg, 40%) (Found: M^+, 135.0679. C_8H_9NO requires *M*, 135.0684); ν_{max}/cm^{-1} 3263 (CH), 2119 (CC) and 1656 (CON); δ_H(250 MHz) 2.2–2.35 (2 H, m, CCH, both rotamers), 3.05 (3 H, s, NMe, minor rotamer), 3.20 (3 H, s, NMe, major rotamer), 3.35 (2 H, d, *J* 3.3, CH_2CO, major rotamer), 3.4 (2 H, d, *J* 3.3, CH_2CO, minor rotamer), 4.15 (2 H, d, *J* 3.3, CH_2N, minor rotamer) and 4.25 (2 H, d, *J* 3.3, CH_2N, major rotamer); δ_C(103 MHz) 26 (CH_2CO, minor rotamer), 26.5 (CH_2CO, major rotamer), 34 (CH_2N, minor rotamer), 35 (CH_2N, major rotamer), 37 (NMe, major rotamer), 40 (NMe, minor rotamer), 72.3 (CCH, major rotamer), 72.4 (CCH, minor rotamer), 72.5 (CCH, minor rotamer), 73 (CCH, major rotamer), 76 (CCH, major rotamer), 76.1 (CCH, minor rotamer), 77.8 (CCH, minor rotamer), 78 (CCH, major rotamer), 166.5 (CO, major rotamer) and 166.6 (CO, minor rotamer); *m/z* 135 (M^+, 26%), 96 ($M^+ - CH_2CCH$, 100), 68 (46), 55 (14) and 41 (32).

***N*-Prop-2-ynylpent-4-ynamide 10.** From pent-4-ynoic acid (816 mg, 8.32 mmol), DCC (1.88 g, 9.15 mmol) and prop-2-ynylamine (458 mg, 8.32 mmol) in dichloromethane (30 cm^3); the mixture was stirred for 6 h at room temperature. Chromatography using light petroleum–ether (1:1) as eluent gave the amide (two rotamers in a 1:1 ratio) as a white solid (940 mg, 82%), mp 185–186 °C (Found: C, 71.1; H, 6.8; N, 10.3. C_8H_9NO requires C, 71.09; H, 6.71; N, 10.36%); ν_{max}/cm^{-1} 3270 (NH + CCH) and 1664 (CON); δ_H(270 MHz) 2.0 (1 H, t, *J* 2.5, CCH, both rotamers), 2.25 (1 H, t, *J* 2.5, CCH, both rotamers), 2.4–2.7 (4 H, m, CH_2CC + CH_2CO, both rotamers), 4.04 (2 H, d, *J* 2.5, CH_2N, one rotamer), 4.06 (2 H, d, *J* 2.5, CH_2N, other rotamer) and 6.0–6.2 (1 H, br s, NH); δ_C(125 MHz) (one rotamer only) 15 (CH_2CC), 29 (CH_2CO), 35 (CH_2N), 69 (CCH), 72 (CCH), 79 (CCH), 82 (CCH) and 171 (CO); *m/z* 136 (MH^+, 100%).

***N*-Methyl-*N*-prop-2-ynylpent-4-ynamide 11.** From pent-4-ynoic acid (400 mg, 4.08 mmol), DCC (925 mg, 4.49 mmol) and *N*-methylprop-2-ynylamine (282 mg, 4.08 mmol) in dichloromethane (25 cm^3); the mixture was stirred for 4 h at room temperature. Chromatography using light petroleum–ether (1:1) as eluent gave the amide (two rotamers in a 2:1 ratio) as a pale yellow oil (522 mg, 86%) (Found: M^+, 149.0840. $C_9H_{11}NO$ requires *M*, 149.0841); ν_{max}/cm^{-1} 2209 (CC), 2119 (CC) and 1654 (CON); δ_H(270 MHz) 2.05 (1 H, t, *J* 2.5, CCH, both rotamers), 2.3 (1 H, t, *J* 2.5, CCH, major rotamer), 2.4 (1 H, t, *J* 2.5, CCH, minor rotamer), 2.5–2.75 (4 H, m, CH_2CO + CH_2CC, both rotamers), 3.05 (3 H, s, NMe, minor rotamer), 3.10 (3 H, s, NMe, major rotamer), 4.1 (2 H, d, *J* 2.5, CH_2N, minor rotamer) and 4.25 (2 H, d, *J* 2.5, CH_2N, major rotamer); δ_C(67.5 MHz) 14.1 (CH_2, major rotamer), 14.2 (CH_2, minor rotamer), 32 (CH_2CO, minor rotamer), 32.2 (CH_2CO, major rotamer), 33 (NMe, minor rotamer), 34 (NMe, major rotamer), 36 (CH_2N, major rotamer), 39 (CH_2N, minor rotamer), 69 (CCH, both rotamers), 72 (CCH, major rotamer), 73 (CCH, minor rotamer), 78 (CCH, minor rotamer), 78.5 (CCH, major rotamer), 83 (CCH, both rotamers), 170.4 (CO, major rotamer) and 170.6 (CO, minor rotamer); *m/z* 150 (MH^+, 100%).

***N*-But-3-ynylpent-4-ynamide 12.** From pent-4-ynoic acid (850 mg, 8.66 mmol), DCC (2.14 g, 10.4 mmol) and but-3-ynylamine (597 mg, 8.66 mmol) in dichloromethane (25 cm^3); the mixture was stirred for 16 h at room temperature. Chromatography using light petroleum–ether (1:1) as eluent gave the amide (two rotamers in a 1:1 ratio) as a white solid (739 mg, 57%), mp 63–64 °C (Found: C, 72.2; H, 7.7; N, 9.5. $C_9H_{11}NO$ requires C, 72.46; H, 7.43; N, 9.39%); ν_{max}/cm^{-1} 2115 (CC) and 1646 (CON); δ_H(270 MHz) 2.0 (2 H, t, *J* 2.5, CCH, both rotamers), 2.4–2.6 (6 H, m, CH_2CO + 2 × CH_2CC, both rotamers), 3.41 (2 H, t, *J* 6, CH_2N, one rotamer), 3.42 (2 H, t, *J* 6, CH_2N, other rotamer) and 6.0 (1 H, br s, NH); δ_C(67.5 MHz) 15 (2 × CH_2, both rotamers), 19 (CH_2CO, both rotamers), 35 (CH_2N, one rotamer), 38 (CH_2N, other rotamer), 69 (2 × CCH, one rotamer), 70 (2 × CCH, other rotamer), 81 (2 × CCH, one rotamer), 83 (2 × CCH, other rotamer) and 171 (CO, both rotamers); *m/z* 148 ($M - H^+$, 9%), 110 ($M^+ - CH_2CCH$, 100) and 53 (41).

***N*-Prop-2-ynylhex-5-ynamide 13.** From hex-5-ynoic acid (1.12 g, 10 mmol), DCC (2.48 g, 12 mmol) and prop-2-ynylamine (661 mg, 12 mmol) in dichloromethane (35 cm^3); the mixture was stirred for 48 h at room temperature. Chromatography using light petroleum–ether (1:1) as eluent gave the amide (two rotamers in a 1:1 ratio) as an oil (434 mg, 29%) (Found: M^+, 149.0833. $C_9H_{11}NO$ requires *M*, 149.0841); ν_{max}/cm^{-1} 1640 (CON); δ_H(400 MHz) 1.9 (2 H, quin, *J* 6.5, CH_2), 2.0 (1 H, t, *J* 2, CCH, both rotamers), 2.24 (1 H, t, *J* 2, CCH, both rotamers), 2.25 (2 H, dt, *J* 2, 6.5, CH_2CC, both rotamers), 2.35 (2 H, t, *J* 6.5, CH_2CO), 4.05 (2 H, d, *J* 2, CH_2N, one rotamer), 4.06 (2 H, d, *J* 2, CH_2N, other rotamer) and 5.7 (1 H, br s, NH); δ_C(103 MHz) 18 (CH_2, both rotamers), 23 (CH_2, both rotamers), 29 (CH_2CO, both rotamers), 35 (CH_2N, both rotamers), 69 (CCH, both rotamers), 72 (CCH, both rotamers), 79 (CCH, both rotamers), 83 (CCH, both rotamers) and 172 (CO, both rotamers); *m/z* 150 (MH^+, 100%).

***N*-Methyl-*N*-prop-2-ynylhex-5-ynamide 14.** From hex-5-ynoic acid (561 mg, 5 mmol), DCC (1.14 g, 5.5 mmol) and *N*-methylprop-2-ynylamine (380 mg, 5.5 mmol) in dichloromethane (25 cm^3); the mixture was stirred for 16 h at room temperature. Chromatography using light petroleum–ether (1:2) as eluent gave the amide (two rotamers in a 2:1 ratio) as an oil (382 mg, 47%) (Found: MH^+, 164.1081. $C_{10}H_{14}NO$ requires *M*, 164.1075); ν_{max}/cm^{-1} 2117 (CC) and 1649 (CON); δ_H(400 MHz) 1.9 (2 H, quin, *J* 6.5, CH_2, both rotamers), 2.0 (1 H, t, *J* 2, CCH, both rotamers), 2.2 (1 H, t, *J* 2, CCH, both rotamers), 2.3 (2 H, dt, *J* 2, 6.5, CH_2CC, both rotamers), 2.45 (2 H, t, *J* 6.5, CH_2CO, major rotamer), 2.55 (2 H, t, *J* 6.5, CH_2CO, minor rotamer), 3.0 (3 H, s, NMe, minor rotamer), 3.1 (3 H, s, NMe, major rotamer), 4.1 (2 H, d, *J* 2, CH_2N, minor rotamer) and 4.25 (2 H, d, *J* 2, CH_2N, major rotamer); δ_C(103 MHz) 18 (CH_2, both rotamers), 23.5 (CH_2, major rotamer), 24 (CH_2, minor rotamer), 31.5 (CH_2CO, minor rotamer), 32 (CH_2CO, major rotamer), 36 (CH_2N, major rotamer), 39 (CH_2N, minor rotamer), 69 (CCH, both rotamers), 72 (CCH, major rotamer), 73 (CCH, minor rotamer), 78 (CCH, minor rotamer), 79 (CCH, major rotamer), 84 (CCH, both rotamers), 172 (CO, major rotamer) and 172.1 (CO, minor rotamer); *m/z* (CI) 181 (MNH_4^+, 15%), 164 (MH^+, 100) and 126 (24).

***N*-But-3-ynylhex-5-ynamide 15.** From hex-5-ynoic acid (897 mg, 8 mmol), DCC (2.06 g, 10 mmol) and but-3-ynylamine (552 mg, 8 mmol) in dichloromethane (30 cm^3); the mixture was stirred for 20 h at room temperature. Chromatography using light petroleum–ether (1:1) as eluent gave the amide (two rotamers in a 1:1 ratio) as a white solid (397 mg, 30%), mp 32–33 °C (Found: MH^+, 164.1065. $C_{10}H_{14}NO$ requires *MH*, 164.1075); ν_{max}/cm^{-1} 2117 (CC) and 1646 (CON); δ_H(270 MHz) 1.85 (2 H, quin, *J* 6.5, CH_2), 2.0 (1 H, t, *J* 2, CCH, both rotamers), 2.05 (1 H, t, *J* 2, CCH, both rotamers), 2.2–2.5 (6 H, m, CH_2CO + 2 × CH_2CC, both rotamers), 3.4 (2 H, t, *J* 6, CH_2N, one rotamer), 3.41 (2 H, t, *J* 6, CH_2N, other rotamer) and 6.25 (1 H, br s, NH); δ_C(67.5 MHz) 18 (CH_2, both rotamers), 20 (CH_2,

both rotamers), 24 (CH_2, both rotamers), 35 (CH_2CO, both rotamers), 38 (CH_2N, both rotamers) 69 (C*C*H, both rotamers), 70 (C*C*H, both rotamers), 82 (C*C*H, both rotamers) and 172 (CO, both rotamers); *m/z* 164 (MH^+, 100%).

General procedure for the co-cyclization of diynamides with methyl prop-2-ynyl ether

A mixture of the diynamide and methyl prop-2-ynyl ether in dry THF was added to a heated (60 °C) solution of nickel(0) reagent (1 equiv.) in THF (approx. 0.3 mol dm^{-3}) under argon prepared according to the literature procedure.[1c] The mixture was then stirred at that temperature for 24 h, cooled to room temperature and quenched with 5 mol dm^{-3} HCl (isoindolinones) or saturated, aqueous NH_4Cl (isoquinolinone). The THF was evaporated on a rotary evaporator and the residue was diluted with water. Extraction with ethyl acetate gave the crude product which was chromatographed using the indicated solvents as eluents.

5- and 6-Methoxymethylisoindolin-1-one 7a. From *N*-prop-2-ynylpropynamide (142 mg, 1.33 mmol) and methyl prop-2-ynyl ether (372 mg, 5.3 mmol). Elution with methanol–ether (1:20) gave the product (two regioisomers in a 1:1 ratio) as an oil (140 mg, 59%) (Found: M^+, 177.0794. $C_{10}H_{11}NO_2$ requires *M*, 177.0790); ν_{max}/cm^{-1} 1679 (CO) and 1590 (C=C); δ_H(270 MHz) 3.3 (3 H, s, OMe, one isomer), 3.35 (3 H, s, OMe, other isomer), 4.35 (2 H, s, CH_2O, both isomers), 4.45 (2 H, s, CH_2N, both isomers), 7.3–7.5 (2 H, m, ArH *m*- and *p*- to CO, both isomers), 7.75 (1 H, m, ArH *o*- to CO, both isomers) and 8.4 (1 H, br s, NH, both isomers); δ_C(125 MHz) 45.5 (CH_2N, one isomer), 45.6 (CH_2N, other isomer), 58.1 (OMe, one isomer), 58.4 (OMe, other isomer), 74.1 (CH_2O, one isomer), 74.3 (CH_2O, other isomer), 122, 122.7, 123.3, 123.6, 127, 131.2, 131.6, 132, 138, 142, 143, 144 and 172 (CO, both isomers); *m/z* 178 (MH^+, 100%) and 162 (M^+ − Me, 58).

5- and 6-Methoxymethyl-*N*-methylisoindolin-1-one 7b. From *N*-methyl-*N*-prop-2-ynylpropynamide (89 mg, 0.73 mmol) and methyl prop-2-ynyl ether (206 mg, 2.94 mmol). Elution with methanol–ether (1:33) gave the product (two regioisomers in a 1:1 ratio) as an oil (46 mg, 34%) (Found: M^+, 192.1030. $C_{11}H_{14}NO_2$ requires *M*, 192.1024); ν_{max}/cm^{-1} 1685 (CO); δ_H(270 MHz) 3.15 (3 H, s, NMe, both isomers), 3.35 (3 H, s, OMe, one isomer), 3.4 (3 H, s, OMe, other isomer), 4.35 (2 H, s, CH_2O, both isomers), 4.5 (2 H, s, CH_2N, both isomers) and 7.3–7.8 (3 H, m, ArH, both isomers); δ_C(125 MHz) 29 (NMe, one isomer), 30 (NMe, other isomer), 51 (CH_2N, one isomer), 52 (CH_2N, other isomer), 58 (OMe, one isomer), 58.3 (OMe, other isomer), 74 (CH_2O, one isomer), 74.2 (CH_2O, other isomer), 121, 122.4, 122.5, 128.3, 128.5, 130.5, 130.7, 131.5, 131.6, 134, 138, 141, 142, 168.2 (CO, one isomer) and 168.3 (CO, other isomer); *m/z* 191 (M^+, 55%), 146 (M^+ − CH_2OMe, 88) and 28 (100).

5- and 6-Methoxymethyl-*N*-benzylisoindolin-1-one 7c. From *N*-benzyl-*N*-prop-2-ynylpropynamide (144 mg, 0.73 mmol) and methyl prop-2-ynyl ether (205 mg, 2.92 mmol). Repeated chromatography with light petroleum–ether (1:1) gave the product (two regioisomers in a 1:1 ratio) as an oil (7 mg, 4%) (Found: M^+, 267.1238. $C_{17}H_{17}NO_2$ requires *M*, 267.1259); ν_{max}/cm^{-1} 1689 (CO), 1493 (C=C) and 1099 (C–O); δ_H(270 MHz) 3.4 (3 H, s, OMe, one isomer), 3.41 (3 H, s, OMe, other isomer), 4.25 (2 H, s, CH_2O, both isomers), 4.45 (2 H, s, CH_2N, one isomer), 4.5 (2 H, s, CH_2N, other isomer), 4.8 (2 H, s, $PhCH_2N$, both isomers), 7.2–7.55 (2 H, m, ArH *m*- and *p*- to CO, both isomers) and 7.85 (1 H, m, ArH *o*- to CO, both isomers); δ_C(125 MHz) 46 (CH_2N, both isomers), 49.5 ($PhCH_2N$, one isomer), 49.6 ($PhCH_2N$, other isomer), 58.1 (OMe, one isomer), 58.3 (OMe, other isomer), 74.1 (CH_2O, one isomer), 74.3 (CH_2O, other isomer), 122.5, 123, 124, 127, 127.6, 127.8, 128, 128.1, 129, 131, 132, 133, 137, 139, 141, 141.5, 142, 168.2 (CO, one isomer) and 168.3 (CO, other isomer); *m/z* 268 (MH^+, 100%) and 91 ($PhCH_2^+$, 18).

5- and 6-Methoxymethyl-*N*-(diphenylmethyl)isoindolin-1-one 7d. From *N*-diphenylmethyl-*N*-prop-2-ynylpropynamide (250 mg, 0.91 mmol) and methyl prop-2-ynyl ether (256 mg, 3.66 mmol). Elution with light petroleum–ether (1:1) gave the product (two regioisomers in a 4:5 ratio) as an oil (198 mg, 63%) (Found: M^+, 343.1570. $C_{23}H_{21}NO_2$ requires *M*, 343.1572); ν_{max}/cm^{-1} 1690 (CO) and 1098 (C–O); δ_H(270 MHz) 3.39 (3 H, s, OMe, minor isomer), 3.4 (3 H, s, OMe, major isomer), 4.2 (2 H, s, CH_2O, both isomers), 4.5 (2 H, s, CH_2N, major isomer), 4.55 (2 H, s, CH_2N, minor isomer), 6.9 (1 H, s, CHN, both isomers), 7.2–7.55 (2 H, m, ArH *m*- and *p*- to CO, both isomers) and 7.85 (1 H, m, ArH *o*- to CO, both isomers); δ_C(125 MHz) 47 (CH_2N, both isomers), 58 (OMe, minor isomer), 58.3 (OMe, major isomer), 59 (CHN, both isomers), 74.1 (CH_2O, minor isomer), 74.2 (CH_2O, major isomer), 122, 122.6, 123, 124, 127, 127.5, 128, 128.5, 128.6, 129, 131, 132, 132.5, 138.5, 139, 141, 141.5, 142 and 168 (CO, both isomers); *m/z* 343 (MH^+, 100%) and 167 (Ph_2CH^+, 18).

6- and 7-Methoxymethyl-*N*-methyl-1,4-dihydroisoquinolin-3(2*H*)-one 9. From *N*-methyl-*N*-prop-2-ynylbutynamide (95 mg, 0.70 mmol) and methyl prop-2-ynyl ether (196 mg, 2.8 mmol). Elution with methanol–ether (1:33) gave the product (two regioisomers in a 1:1 ratio) as an oil (85 mg, 59%) (Found: M^+, 205.1104. $C_{12}H_{15}NO_2$ requires *M*, 205.1103); ν_{max}/cm^{-1} 1655 (CO); δ_H(400 MHz) 3.1 (3 H, s, NMe, both isomers), 3.4 (3 H, 2 × s, OMe, both isomers), 3.6 (2 H, 2 × s, CH_2CO, both isomers), 4.45 (2 H, 2 × s, CH_2O, both isomers), 4.5 (2 H, s, CH_2N, both isomers) and 7.1–7.3 (3 H, m, ArH); δ_C(100 MHz) 34 (NMe, both isomers), 36.7 (CH_2CO, one isomer), 36.8 (CH_2CO, other isomer), 52.7 (CH_2N, one isomer), 52.9 (CH_2N, other isomer), 58 (OMe, both isomers), 74 (CH_2O, both isomers), 124, 125, 126, 126.5, 127, 127.5, 130, 131, 131.5, 132, 137, 138 and 168 (CO, both isomers); *m/z* 206 (MH^+, 100%).

***N*-[Bis(methoxymethyl)benzyl]pent-4-ynamide 16.** From *N*-prop-2-ynylpent-4-ynamide (123 mg, 0.90 mmol) and methyl prop-2-ynyl ether (252 mg, 3.6 mmol). Elution with methanol–ether (1:20) gave the product as a mixture of regioisomers as an oil (20 mg, 7%) (Found: M^+, 275.1522. $C_{16}H_{21}NO_3$ requires *M*, 275.1523); δ_H(400 MHz) 1.95 (1 H, t, *J* 3, CCH, one isomer), 2.05 (1 H, t, *J* 3, CCH, other isomer), 2.35–2.6 (4 H, m, CH_2CO + CH_2CC, both isomers), 3.4 (6 H, more than one s, MeO, both isomers), 4.5 (2 H, 2 × s, CH_2N, both isomers), 6.0 (1 H, br s, NH, one isomer), 6.4 (1 H, br s, NH, other isomer) and 7.2–7.4 (3 H, m, ArH); *m/z* (EI) 276 (MH^+, 33%), 243 (M^+ − MeOH, 81), 178 (48), 163 (100), 133 (49) and 131 (60); *m/z* (CI) 293 (MNH_4^+, 25%) and 276 (MH^+, 100).

Crystal data for 3e. $C_{23}H_{25}NO_5$, M_r = 395.4, monoclinic, $P2_1/n$, Z = 4, a = 6.139(2), b = 40.099(9), c = 8.657(2) Å, β = 101.55(2)°, V = 2087.8(7) Å^3, D_c = 1.26 g cm^{-3}, λ(Cu-Kα) = 1.541 78 Å, μ = 7.24 cm^{-1}, F(000) = 840, T = 293 K. A single crystal of dimensions 0.15 × 0.60 × 0.60 mm was used. Intensity data were collected on a Siemens P4 diffractometer using graphite monochromated Cu-Kα radiation. 2391 Independent reflections were measured using ω-scans ($2\theta_{max}$ = 116°), and of these 1826 had $|F_o| > 4.0\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarization factors, but not for absorption. The structure was solved by direct methods and all full occupancy non-hydrogen atoms were refined anisotropically. A ΔF map revealed the presence of disorder (60:40) in the terminal methyl groups of the ester functions. The minor occupancy atoms were refined isotropically. Hydrogen atoms were placed in calculated positions, assigned isotropic thermal parameters $U(H) = 1.2U_{eq}(C)$ and allowed to ride on their parent carbon atoms. Full-matrix least-squares refinement on F_o converged to give R = 0.052, R_w = 0.058 ($w^{-1} = \sigma^2(F) + 0.0005F^2$), for 259 refined parameters. The largest and mean Δ/σ were 0.004 and 0.000, and the largest difference peak/hole were 0.19 and −0.17 e A^{-3} respectively. Computations were carried out on a 486 PC using the

SHELXTL-PC program system.[14] Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. For details, see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1.

Acknowledgements

One of us (S. L.-W.) thanks the SERC and SmithKline Beecham for a CASE award.

References

1 (*a*) E. C. Colthup and L. S. Meriwether, *J. Org. Chem.*, 1961, **26**, 5169; (*b*) P. Bhatarah and E. H. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2603; (*c*) P. Bhatarah and E. H. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2163.
2 G. P. Chiusoli, L. Pallini and G. Terenghi, *Transition Met. Chem.*, 1983, **8**, 189.
3 Y. Sato, T. Nishimata and M. Mori, *J. Org. Chem.*, 1994, **59**, 6133.
4 Preliminary report: M. Duckworth, E. H. Smith and S. Lee-Wong, in *Organometallic Reagents in Organic Synthesis*, eds. J. H. Bateson and M. B. Mitchell, Academic Press, London, 1994.
5 L. A. La Planche and M. T. Rogers, *J. Am. Chem. Soc.*, 1963, **85**, 3728.
6 W. E. Stewart and T. H. Siddall, *Chem. Rev.*, 1970, **70**, 517.
7 N. J. McCorkindale and A. W. McCulloch, *Tetrahedron*, 1971, **27**, 4653; G. Deak, K. Gall-Istok and L. Sterk, *Synthesis*, 1975, 393.
8 V. Wolf, *Annalen*, 1952, **576**, 35.
9 W. R. Jackson, P. Perlmutter and A. J. Smallridge, *Aust. J. Chem.*, 1988, **41**, 1201; I. Marszak and A. Marszak-Fleury, *C.R. Hebd. Seances Acad. Sci.*, 1955, **241**, 704.
10 L. Engman, *J. Org. Chem.*, 1991, **56**, 3425.
11 B. Henke, A. J. Kouklis and C. H. Heathcock, *J. Org. Chem.*, 1992, **57**, 7056.
12 G. E. Hennion and R. H. Ode, *J. Org. Chem.*, 1966, **31**, 1975.
13 G. P. Chiusoli, M. Costa, P. Reverberi and M. G. Terenghi, *Transition Met. Chem.*, 1989, **14**, 238.
14 G. M. Sheldrick, SHELXTL-PC (Version 4.2), 1991, an integrated system for solving, refining and displaying crystal structures from diffraction data, Siemens Analytical Instruments Inc., WI.

Paper 5/05747G
Received 31*st August* 1995
Accepted 18*th December* 1995