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Aust. J. Chem. **2005**, *58*, 368–374

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Preparation and Cyclization of Some *N*-(2,2-Dimethylpropargyl) Homo- and Heteroaromatic Amines and the Synthesis of Some Pyrido[2,3-*d*]pyrimidines

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The Cu(I) catalyzed cyclization of *o*-substituted *N*-(2,2-dimethylpropargyl)anilines yields 8-substituted 2,2-dimethyl-1,2-dihydroquinolines, while *m*-substituted analogues provide a mixture of 5- and 7-substituted dihydroquinoline systems. This reaction can be extended to 2-amino-*N*-(2,2-dimethylpropargyl)anthracene, yielding a dihydronaphtho[2,3-*f*]quinoline product, and to aminoquinoline derivatives, which yield substituted phenanthroline products. Pyridine analogues did not cyclize, apparently because of complexation with the copper reagent.

An alternative synthetic approach to these cyclized products, when complexation may be a problem, is illustrated by the following example. 2-Chloro-4-*N*-(2,2-dimethylpropargyl)pyrimidine was reduced using a Lindlar catalyst to the corresponding alkene which did not undergo an amino-Claisen rearrangement. However, the 5-bromopyrimidine alkene analogue underwent addition with phenylselanyl bromide to give a product that cyclized, using butyllithium, to a pyrido[2,3-*d*]pyrimidine selenium-containing product from which the selenium moiety could be removed to yield either a dihydro- or a tetrahydro-pyrido[2,3-*d*]pyrimidine system. A Heck reaction on the 5-bromopyrimidine alkene gave a 5-methylene-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine.

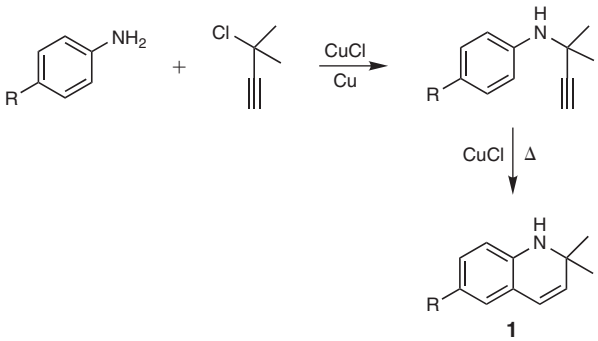
Manuscript received: 29 October 2004.
Final version: 17 February 2005.

Introduction

We have recently described the synthesis (Scheme 1) of 6-substituted 2,2-dimethyl-1,2-dihydroquinolines **1** using a Cu(I) catalyzed cyclization of 4-substituted *N*-(2,2-dimethylpropargyl)anilines.[1,2] We have shown that these dihydroquinolines are useful for the preparation of a range of 3- and 4-substituted and 3,4-disubstituted tetrahydroquinolines.[1] We have also utilized these reactions as part of an approach to the synthesis of analogues of virantmycin.[3]

A wide range of 4-substituted *N*-(2,2-dimethylpropargyl)-anilines can be cyclized by this process, with electron-withdrawing substituents significantly slowing the rate of the cyclization but otherwise having no effect on the process.[1] Our studies towards the preparation of virantmycin analogues showed that while 2,2-dimethylpropargyl chlorides couple readily to a range of 4-substituted anilines this coupling reaction is sensitive to the size of the substituents at the 2-position, with 2,2-dibutylpropargyl chlorides not coupling.[2]

In this paper we examine further the scope of the cyclization of *N*-(2,2-dimethylpropargyl)anilines by describing our results on the cyclization of 2- and 3-substituted aniline derivatives and on the cyclization of similarly substituted heterocyclic amine derivatives rather than those from anilines. The expected products from the cyclization of the substituted heterocyclic amine derivatives would provide analogues of virantmycin with extra heteroatoms in the analogue ring structures.



Scheme 1.

Results and Discussion

Synthesis of the N-*(2,2-Dimethylpropargyl) Aromatic Amines*

Both *o*- and *m*-toluidine and *o*-anisidine coupled readily with 3-chloro-3-methylbut-1-yne[4] to give the products **2**, **3**, and **4** respectively (Scheme 2), using the same conditions developed for the 4-substituted anilines; these results indicate that the coupling process was not affected by an adjacent *ortho* group. *m*-Phenylenediamine also coupled readily to give **5** as an unstable oil. Because of the problem of carcinogenicity we chose not to extend the investigation to aminonaphthalenes, but we did investigate two anthracene-based compounds. 2-Aminoanthracene coupled readily to give **6**. However, 2-aminoanthraquinone did not react with the chloro alkyne,

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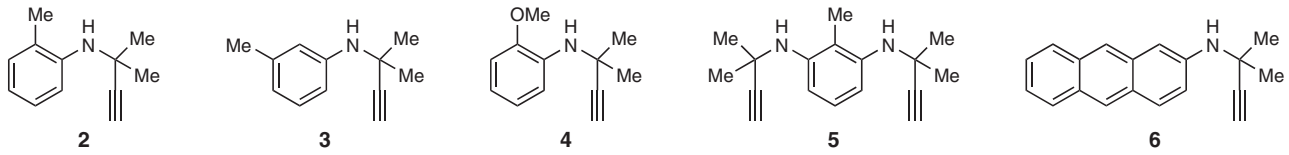
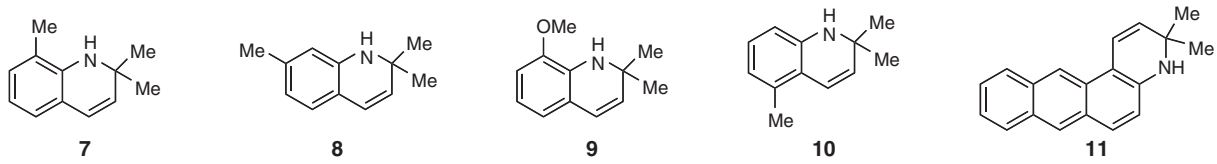


Scheme 2.



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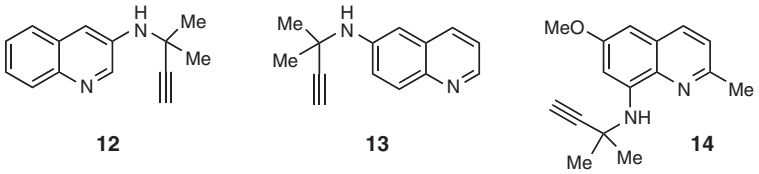
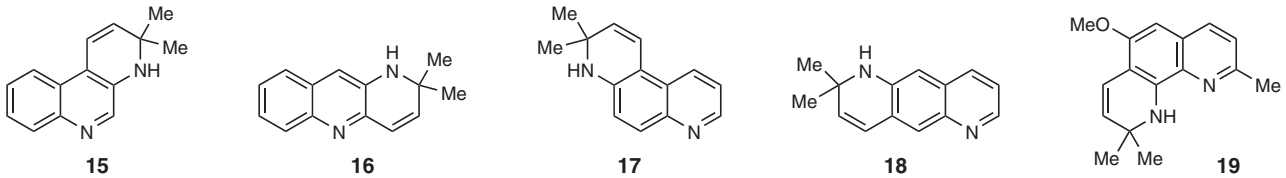


Scheme 4.



Scheme 5.

even after an extended reaction period. Presumably this lack of reactivity is a consequence of the deactivating influence of one of the carbonyl groups on the amine.

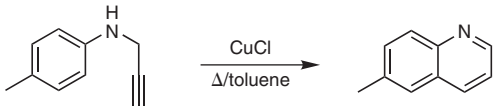
Cyclization of the N-*(2,2-Dimethylpropargyl) Aromatic Amines*

Both of the *ortho*-substituted anilines **2** and **4** cyclized using our standard conditions to give the corresponding dihydroquinolines **7** and **9** respectively (Scheme 3), in moderate yields. As expected, the *meta*-substituted aniline derivative **3** cyclized in the two possible ways to give a 1 : 1 mixture of **8** and **10**. The *m*-phenylenediamine derivative **5** gave only an intractable product with no signals attributable to the double-bond hydrogens of a dihydroquinoline system in the ^{1}H NMR spectrum of the total product. The 2-aminoanthracene derivative **6** cyclized readily to give only the naphthoquinoline **11** in moderate yield. The formation of only one of the two possible cyclization products is presumably a consequence of bond fixation in the anthracene system. Other examples of cyclization preference for this reason are described below.

Preparation and Cyclization of N-*(2,2-Dimethylpropargyl) Heterocyclic Aromatic Amines*

It was expected that the preparation of the *N*-(2,2-dimethylpropargyl) derivatives of heterocyclic aromatic amines could be complicated, in some cases, by the possibility of coordination to the copper used in the coupling step. This was indeed the case with 2- and 4-aminopyridine, and in both cases a dark precipitate was obtained from the reaction mixture; some starting material was also recovered. Workup of the precipitate obtained from the reaction using 4-aminopyridine and EDTA (ethylenediaminetetraacetic acid) returned 4-aminopyridine only. Surprisingly, it has been claimed that 4-aminopyridine underwent the coupling reaction, although no details of the product were provided.[5] Because of suggestions[6,7] that the actual reagent in these coupling reactions was a 1-chloroallene, formed by rearrangement of the carbocation from the propargyl chloride, the reaction of 2-aminopyridine with 1-bromo-3-methylbuta-1,2-diene was investigated as an alternative approach, both in the absence and presence of copper(I). In each case both starting materials were recovered after workup, with no sign of a coupled product.

Three aminoquinolines were coupled with 3-chloro-3-methylbut-1-yne utilizing the same conditions used for the aromatic amines described above to give the corresponding *N*-substituted quinolines **12**, **13**, and **14** (Scheme 4). The poor yield obtained in the case of **14** may be due, in part, to complexation of the starting material and/or the product with copper.



20 **21**

Scheme 6.

The *N*-substituted aminoquinolines **12**, **13**, and **14** cyclized, using the standard conditions, to give moderate yields of a single phenanthroline product, **15**, **17**, and **19** (Scheme 5) respectively in each case. That the cyclization of **12** yielded **15**, rather than **16**, was shown by the ^{1}H NMR spectrum of the product which showed a singlet at δ 8.32 attributable to the hydrogen at position 2 which is deshielded by the adjacent aromatic ring nitrogen (the corresponding signal in **12** is at δ 8.48). Structure **16** would not be expected to have a signal in this region. The signals for the double-bond hydrogens of **15** are at δ 5.74 and 6.94. The former is a doublet of doublets due to coupling (10 Hz) to the adjacent alkene hydrogen as well as a W-coupling (2.2 Hz) to the NH. The starting material **7** has a signal at 7.63 (*J* 2.9 Hz), due to the hydrogen at position 4; a signal of this type is absent from the spectrum of the product **15**.

Cyclization of **13** also formed only one product, the phenanthroline **17**, whose structure was confirmed by its ^{1}H NMR spectrum, which showed two doublets in the aromatic region (δ 6.93 and 7.65, each with a coupling constant of 9 Hz) due to the hydrogens (H5 and H6) of the benzenoid portion of the structure. In addition, the three signals for the hydrogens of the heterocyclic aromatic ring (H9, H10, and H11) appeared at δ 8.58 (*J* 4.2 Hz), 7.25 (*J* 4.2, 8.5 Hz), and 8.15 (*J* 8.5 Hz) respectively. The two alkene hydrogens appeared as a doublet at δ 6.87 (*J* 9.9 Hz) and a doublet of doublets at 5.35 (*J* 2.0, 9.9 Hz) for H1 and H2 respectively. The small coupling observed for H1 is presumably caused by a W-coupling to the NH. The alternative product, **18**, would be expected to show two singlets for H5 and H10. The formation of only one of two possible products in the cyclizations of **12** and **13** can be attributed to bond fixation.

Cyclization of **14** gave only one product **19** as expected, which showed signals at δ 5.48 (*J* 2.2, 9.8 Hz) and 6.73 (*J* 9.8 Hz) for the alkene hydrogens, H8 and H9 respectively. Again, the small coupling observed for H9 is probably due to a W coupling with the adjacent NH. The low yield obtained for this reaction may also be, in part, caused by complexation of the starting material and/or the product with copper.

A propargylaniline **20**, unsubstituted at position 2 of the propargyl chain, was prepared using the standard procedure.[2] The cyclization procedure for this material, which yielded 6-methylquinoline **21** (Scheme 6) had to be modified since it was found that as soon as any quinoline was produced it formed a complex with the copper present, thus removing copper from the catalytic cycle. The cyclization was carried out with one equivalent of cuprous chloride. The workup procedure for the reaction was also modified as the resulting copper–quinoline complex needed to be broken up using EDTA.

*Synthesis of the Pyrido[2,3-*d*]pyrimidines **29–31***

Our experience with the 2-aminopyridine system suggested that it would be difficult to cyclize a pyrimidine propargylamine by using copper catalysis, and so we approached the synthesis of the desired cyclized product in a different way. The pyrimidine derivative **22** was easier to prepare by a nucleophilic attack on 2,4-dichloropyrimidine, rather than by the general method used for the aniline systems.[2] Accordingly the propargylamine **23** was prepared and treated with 2,4-dichloropyrimidine to give **22** as the major product in a mixture that contained two regioisomers (ratio 9 : 1; Scheme 7).

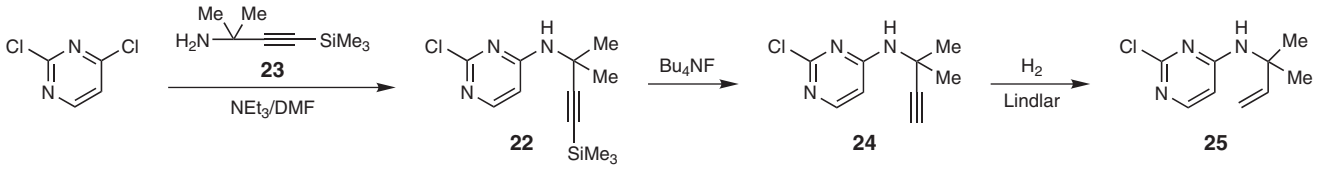
The major isomer was purified by chromatography and its structure shown to be **22** by an X-ray crystal structure determination.[8] The protecting trimethylsilyl group was removed with tetrabutylammonium fluoride and the alkyne product **24** was reduced by catalytic hydrogenation with a Lindlar catalyst to give the alkene **25** which failed to undergo an amino-Claisen rearrangement using conditions successfully employed for related aniline systems.[2] Consequently, the sequence was repeated with 5-bromo-2,4-dichloropyrimidine (Scheme 8) to yield the alkene **27**. In this case the precaution of protecting the alkyne functionality as its trimethylsilyl derivative was found to be unnecessary. A Heck reaction on **27** gave only the 1,5-*exo* cyclization product **28** as indicated by a ^{13}C DEPT NMR spectrum which showed that the two alkene carbons at δ 137.6 and 115.4 were quarternary and secondary respectively. The alkene **27** reacted readily with phenylselanyl bromide to give an unstable addition product, which was cyclized, in situ, by the addition of butyllithium to yield the bicyclic selenide **29**. The size of the newly created ring, and hence the mode of addition of the phenylselanyl bromide, was confirmed by a reductive removal of the phenylselanyl group to give a product **30** whose ^{1}H NMR spectrum showed the presence of two adjacent methylene groups. The phenylselanyl group in **29** could be oxidatively removed, in poor yield, with either sodium periodate or hydrogen peroxide to give the desired dihydropyrido[2,3-*d*]pyrimidine **31**.

Conclusions

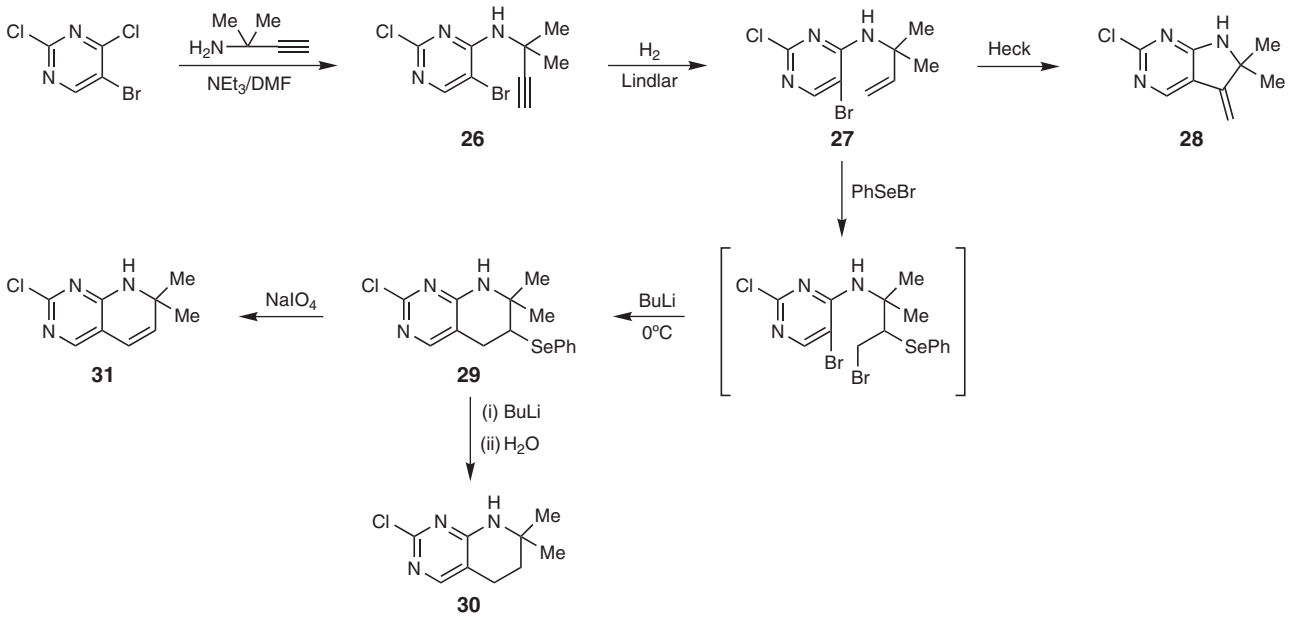
The cyclization of *p*-substituted *N*-(2,2-dimethylpropargyl) anilines to yield substituted 2,2-dimethyl-1,2-dihydroquinolines can be extended to *o*- and *m*-substituted analogues, although in the latter case two regioisomers are produced. The reaction can also be used with a 2-aminoanthracene analogue, to yield 3,3-dimethyl-3,4-dihydronaphtho[2,3-*f*]quinoline. However, 2-aminoanthraquinone did not form the precursor necessary for the cyclization process.

While *N*-(2,2-dimethylpropargyl)quinolines can be readily prepared and cyclized to substituted phenanthrolines, pyridine systems do not form the propargyl derivative necessary for the cyclization, apparently because complexation of the amine with the copper(I) reagent prevents the coupling process.

In the case of an aminopyrimidine system, which presumably would be likely to suffer from the same



Scheme 7.



Scheme 8.

complexation observed with aminopyridines, the cyclization product was prepared by a different approach. The *N*-(2,2-dimethylpropargyl) derivative of 4-amino-5-bromo-2-chloropyrimidine was reduced to an alkene which underwent an addition reaction with phenylselanyl bromide to give an adduct which was cyclized, using butyllithium, and the selenium moiety removed, using an oxidative elimination process, to provide a substituted pyrido[2,3-*d*]pyrimidine in poor yield. A Heck reaction on the alkene gave a substituted 5-methylene-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine. These last two reactions further illustrate the synthetic utility of *N*-(2,2-dimethylpropargyl) derivatives of heterocyclic amines.

Experimental

General Experimental Conditions

Melting points were determined on a Kofler hot stage apparatus equipped with a Reichert microscope and are uncorrected. Infrared spectra were recorded on a Jasco A102 grating spectrometer. Proton NMR spectra (δ_H) were recorded on a Bruker ACP300 spectrometer operating at 300 MHz in (D)chloroform solution (unless otherwise stated) using tetramethylsilane as an internal standard. Chemical shifts are quoted as δ in parts per million and coupling constants (*J*) are given in Hertz. Electron-impact mass spectra (*m/z*) were recorded at 70 eV on a VG ZAB 2HF spectrometer. Microanalyses were performed by the Canadian Microanalytical Service Ltd or by the Chemical and Microanalytical Service Pty Ltd, Melbourne. Accurate mass measurements (HRMS) were made using electron impact on either an AEI MS3074 spectrometer or by the University of Melbourne on a JEOL AX505H spectrometer. Flash chromatography refers to nitrogen pressure driven rapid chromatography[9] using Merck silica gel, pore diameter 60 Å.

General Procedure for the Coupling of 3-Chloro-3-methylbut-1-yne with Aromatic Amines

A solution of 3-chloro-3-methylbut-1-yne[4] (approx. 7 mmol) in tetrahydrofuran (1 mL) was added slowly to a stirred mixture of the corresponding aromatic amine (approx. 5 mmol), cuprous chloride (50 mg), copper bronze powder (50 mg), and triethylamine (approx. 7 mmol) in tetrahydrofuran (5 mL) and water (0.5 mL), and the resulting mixture stirred at room temperature under an atmosphere of nitrogen for 30–120 min. Water (10 mL) was added and the organic phase separated and combined with the dichloromethane extracts of the aqueous phase. The combined organic extracts were dried and the solvent was removed. The residue was purified by flash chromatography. By this means the following compounds were prepared.

2-Methyl-N-*(2-methylbut-3-yn-2-yl)aniline* **2** was obtained from *o*-toluidine as an orange oil (28%) after elution with light petroleum/ethyl acetate (85 : 15) (Found: 173.1197. $C_{12}H_{15}N$ requires 173.1204). ν_{max} ($CDCl_3$)/cm^{-1} 3415, 3300, 1600, 1505. δ_H 7.29 (1H, dd, *J* 0.9, 8.2, ArH), 7.10 (2H, m, ArH), 6.71 (1H, dt, *J* 0.9, 7.3, ArH), 3.53 [1H, br s (exchanges with D_2O), NH], 2.37 (1H, s, alkyne H), 2.13 (3H, s, ArMe), 1.65 (6H, s, Me). *m/z* 173 (41%, M), 158 (100), 143 (25), 107 (85), 106 (77).

3-Methyl-N-*(2-methylbut-3-yn-2-yl)aniline* **3** was obtained from *m*-toluidine as a red oil (83%) after elution with light petroleum/ethyl acetate (85 : 15) (Found: 173.1203. $C_{12}H_{15}N$ requires 173.1204). ν_{max} ($CDCl_3$)/cm^{-1} 3400, 3300, 1605, 1510. δ_H 7.09 (1H, t, *J* 7.7, ArH), 6.78 (1H, dd, *J* 2.3, 8.3, ArH), 6.73 (1H, br s, ArH), 6.62 (1H, d, *J* 7.7, ArH), 3.61 [1H, br s (exchanges with D_2O), NH], 2.36 (1H, s, alkyne H), 2.29 (3H, s, ArMe), 1.60 (6H, s, Me). *m/z* 173 (65%, M), 158 (100), 143 (10), 107 (44).

2-Methoxy-N-*(2-methylbut-3-yn-2-yl)aniline* **4** was obtained from *o*-anisidine as a pale orange oil (46%) after elution with light petroleum/ethyl acetate (85 : 15) (Found: 189.1158. $C_{12}H_{15}NO$ requires 189.1154). ν_{max} ($CDCl_3$)/cm^{-1} 3420, 3300, 1600, 1505 1225. δ_H 7.27

(1H, dd, *J* 1.5, 7.9, ArH), 6.88 (1H, dt, *J* 1.5, 7.9, ArH), 6.74 (2H, m, ArH), 4.35 [1H, br s (exchanges with D_2O), NH], 3.83 (3H, s, OMe), 2.36 (1H, s, alkyne H), 1.64 (6H, s, Me). *m/z* 189 (43%, M), 174 (100), 159 (12), 144 (23), 123 (54).

N,N′-*Bis-(2-methylbut-3-yn-2-yl)*-m-*phenylenediamine* **5** was obtained from *m*-phenylenediamine as an unstable orange oil (31%) after elution with light petroleum/ethyl acetate (60 : 40) (Found: 240.1615. $C_{16}H_{20}N_2$ requires 240.1626.) δ_H 6.98 (1H, t, *J* 8.1, ArH), 6.72 (1H, t, *J* 2.3, ArH), 6.32 (2H, dd, *J* 2.3, 8.1, ArH), 3.61 [2H, br s (exchanges with D_2O), NH], 2.36 (2H, s, alkyne H), 1.61 (12H, s, Me). *m/z* 240 (95%, M), 225 (100), 210 (25), 209 (30), 173 (90), 159 (75).

2-Amino-N-*(2-methylbut-3-yn-2-yl)anthracene* **6** was obtained from 2-aminoanthracene (obtained by reduction of 2-aminoanthraquinone with Zn/NaOH[10]) as orange needles (22%), mp 85–87°C, after elution with light petroleum/ethyl acetate (80 : 20) and crystallization from dichloromethane/light petroleum (Found: 259.1353. $C_{19}H_{17}N$ requires 259.1361). ν_{max} ($CDCl_3$)/cm^{-1} 3415, 3300, 1625, 1510. δ_H 8.23 (1H, s, ArH), 8.19 (1H, s, ArH), 7.88 (2H, m, ArH), 7.79 (1H, d, *J* 9.0, ArH), 7.35 (3H, m, ArH), 6.95 (1H, dd, *J* 2.3, 9.0, ArH), 3.91 [1H, br s (exchanges with D_2O), NH], 2.45 (1H, s, alkyne H), 1.70 (6H, s, Me). *m/z* 259 (50%, M), 244 (72), 193 (69), 165 (100), 84 (29).

3-Amino-N-*(2-methylbut-3-yn-2-yl)quinoline* **12** was obtained from 3-aminoquinoline as orange prisms (63%), mp 102–104°C, after elution with light petroleum/ethyl acetate (35 : 65) and crystallization from dichloromethane/light petroleum. ν_{max} (CH_2Cl_2)/cm^{-1} 3650, 3300, 1600, 1505, 1550. δ_H 8.48 (1H, d, *J* 2.9, ArH), 7.95 (1H, m, ArH), 7.68 (1H, m, ArH), 7.63 (1H, d, *J* 2.9, ArH), 7.45 (2H, m, ArH), 4.08 [1H, br s (exchanges with D_2O), NH], 2.44 (1H, s, alkyne H), 1.69 (6H, s, Me). *m/z* 210 (55%, M), 195 (80), 168 (20), 144 (90), 176 (30), 69 (100).

6-Amino-N-*(2-methylbut-3-yn-2-yl)quinoline* **13** was obtained from 6-aminoquinoline (obtained from 6-nitroquinoline by reduction with H_2/Pd–C) as an orange oil (28%) after elution with dichloromethane/methanol (95 : 5) (Found: 210.1152. $C_{14}H_{14}N_2$ requires 210.1157). ν_{max} ($CDCl_3$)/cm^{-1} 3390, 3300, 1610, 1505, 1540. δ_H 8.60 (1H, d, *J* 3.0, ArH), 7.96 (1H, dd, *J* 1.1, 8.3, ArH), 7.89 (1H, d, *J* 9.1, ArH), 7.22 (3H, m, ArH), 4.29 [1H, br s (exchanges with D_2O), NH], 2.44 (1H, s, alkyne H), 1.67 (6H, s, Me). *m/z* 211 (40%, M + H), 196 (100), 144 (55), 116 (15).

8-Amino-6-methoxy-2-methyl-N-*(2-methylbut-3-yn-2-yl) quinoline* **14** was obtained from 8-amino-6-methoxy-2-methylquinoline[11] as off-white prisms (12%), mp 110–111°C, after elution with dichloromethane and crystallization from dichloromethane/light petroleum (Found: 254.1406. $C_{16}H_{18}N_2O$ requires 254.1419). δ_H 7.82 (1H, d, *J* 8.3, ArH), 7.18 (1H, d, *J* 8.3, ArH), 6.95 (1H, d, *J* 2.5, ArH), 6.43 [1H, br s (exchanges with D_2O), NH], 6.38 (1H, d, *J* 2.5, ArH), 3.89 (3H, s, OMe), 2.64 (3H, s, ArMe), 2.41 (1H, s, alkyne H), 1.77 (6H, s, Me). *m/z* 254 (40%, M), 239 (100), 213 (10), 196 (10), 188 (20).

General Procedure for the Cyclization of N-*(2,2-Dimethylpropargyl)anilines*

A mixture of the *N*-propargylaniline (approx. 2 mmol) and cuprous chloride (50 mg) in toluene (5 mL) was refluxed under an atmosphere of nitrogen for 30–90 min. The reaction mixture was cooled, water (5 mL) added, and the organic phase separated and combined with the dichloromethane extracts of the aqueous phase. The combined organic extracts were dried and the solvent was removed. The residue was purified by flash chromatography. By this means the following compounds were prepared.

2,2,8-Trimethyl-1,2-dihydroquinoline **7** was obtained as a yellow oil (52%) after elution with light petroleum/ethyl acetate (85 : 15) (Found: 173.1191. $C_{12}H_{15}N$ requires 173.1204). ν_{max} ($CDCl_3$)/cm^{-1} 3415, 1630, 1600, 1505. δ_H 6.86 (1H, d, *J* 7.5, ArH), 6.78 (1H, d, *J* 7.5, ArH), 6.51 (1H, t, *J* 7.5, ArH), 6.26 (1H, d, *J* 9.7, C=CH), 5.45 (1H, d, *J* 9.7, C=CH), 3.50 [1H, br s (exchanges with D_2O), NH], 2.07 (3H, s, ArMe), 1.32 (6H, s, Me). *m/z* 173 (2%, M), 158 (100), 157 (24).

2,2-Dimethyl-8-methoxy-1,2-dihydroquinoline **8** was obtained as a yellow oil (63%) after elution with light petroleum/ethyl acetate (85 : 15) (Found: 189.1150. $C_{12}H_{15}NO$ requires 189.1154). ν_{max} ($CDCl_3$)/cm^{-1} 3400, 1630, 1600, 1500. δ_H 6.58 (3H, m, ArH), 6.26 (1H, d, *J* 9.7, C=CH), 5.45 (1H, d, *J* 9.7, C=CH), 4.17 [1H, br s (exchanges with D_2O), NH], 3.81 (3H, s, OMe), 1.31 (6H, s, Me). *m/z* 189 (9%, M), 174 (100), 159 (46), 131 (14).

2,2,5- and 2,2,7-Trimethyl-1,2-dihydroquinoline **10** and **8**, respectively, were obtained as a yellow oil (70%) after elution with light petroleum/ethyl acetate (85 : 15) which was an inseparable 1 : 1 mixture of the 2,2,5- and 2,2,7-trimethyl isomers (Found: 173.1196. $C_{12}H_{15}N$ requires 173.1204). ν_{max} ($CDCl_3$)/cm^{-1} 3400, 1640 1620, 1600, 1500. δ_H 6.85 (1H, t, *J* 7.7, ArH), 6.77 (1H, d, *J* 7.5, ArH), 6.43 (3H, m, ArH and C=CH), 6.25 (1H, m, ArH), 6.23 (1H, br s, ArH), 5.50 (1H, d, *J* 9.9, C=CH), 5.40 (1H, d, *J* 9.7, C=CH), 3.60 [2H, br s (exchanges with D_2O), NH], 2.24 (3H, s, ArMe), 2.20 (3H, s, ArMe), 1.29 [12H, s, ArMe (2 Me for each isomer)]. *m/z* 173 (12%, M), 158 (100).

*3,3-Dimethyl-3,4-dihydronaphtho[2,3-*f*]quinoline* **11** was obtained as a viscous orange oil (55%) after elution with light petroleum/ethyl acetate (85 : 15) (Found: 259.1360. $C_{19}H_{17}N$ requires 259.1361). ν_{max} ($CDCl_3$)/cm^{-1} 3435, 1630, 1555, 1540. δ_H 8.31 (1H, s, ArH), 8.18 (1H, s, ArH), 7.87 (2H, t, *J* 8.1, ArH), 7.68 (1H, d, *J* 9.0, ArH), 7.34 (2H, m, ArH), 7.13 (1H, d, *J* 9.8 Hz, C=CH), 6.74 (1H, d, *J* 9.0, ArH), 5.54 (1H, dd, *J* 1.1, 9.8, C=CH), 3.92 [1H, br s (exchanges with D_2O), NH], 1.36 (6H, s, Me). *m/z* 259 (11%, M), 244 (88), 122 (16), 86 (64), 84 (100).

3,3-Dimethyl-3,4-dihydro-4,6-phenanthroline **15** was obtained as an unstable orange oil (33%) after elution with light petroleum/ethyl acetate (25 : 75). δ_H 8.32 (1H, br s, ArH), 7.92 (1H, d, *J* 8.7 Hz, ArH), 7.83 (1H, d, *J* 9.3, ArH), 7.42 (2H, m, ArH), 6.94 (1H, d, *J* 10.0, C=CH), 5.74 (1H, dd, *J* 2.2, 10.0, C=CH), 4.16 [1H, br s (exchanges with D_2O), NH], 1.37 (6H, s, Me).

3,3-Dimethyl-3,4-dihydro-4,7-phenanthroline **17** was obtained as a yellow oil (42%) after elution with dichloromethane/methanol (95 : 5) (Found: 210.1146. $C_{14}H_{14}N_2$ requires 210.1157). ν_{max} (CH_2Cl_2)/cm^{-1} 3370, 1620, 1590, 1540, 1500. δ_H 8.58 (1H, d, *J* 4.2, ArH), 8.15 (1H, d, *J* 8.5, ArH), 7.65 (1H, d, *J* 9.0, ArH), 7.25 (1H, dd, *J* 4.2, 8.5, ArH), 6.93 (1H, d, *J* 9.0, ArH), 6.87 (1H, d, *J* 9.9, C=CH), 5.35 (1H, dd, *J* 2.0, 9.9, C=CH), 4.23 [1H, br s (exchanges with D_2O), NH], 1.34 (6H, s, Me). *m/z* 211 (15%, M + H), 196 (100), 195 (20), 86 (35), 84 (60).

6-Methoxy-2,9,9-trimethyl-9,10-dihydro-1,10-phenanthroline **19** was obtained as a glassy, red-brown solid, (30%), mp 78–79°C (dec.), after elution with dichloromethane (Found: 254.1425. $C_{16}H_{18}N_2O$ requires 254.1425). ν_{max} ($CDCl_3$)/cm^{-1} 3300, 1620, 1595, 1500, 1550. δ_H 7.74 (1H, d, *J* 8.3, ArH), 7.10 (1H, d, *J* 8.3, ArH), 6.73 (1H, d, *J* 9.8, C=CH), 6.25 (1H, s, ArH), 5.94 [1H, br s (exchanges with D_2O), NH], 5.48 (1H, dd, *J* 2.2, 9.8, C=CH), 2.64 (3H, s, ArMe), 1.41 (6H, s, Me). *m/z* 254 (11%, M), 239 (100), 224 (36), 213 (48), 196 (23), 170 (32).

N-*Propargyl-4-methylaniline* **20** was obtained in the following way. Propargyl bromide (0.37 mL, 4.2 mmol) was added dropwise under an atmosphere of nitrogen to a stirred mixture of *p*-toluidine (0.45 g, 4.2 mmol) and potassium carbonate (0.87 g, 6.3 mmol) in dichloromethane (10 mL) and the resulting mixture stirred at room temperature under an atmosphere of nitrogen for 24 h. Water (10 mL) was added and the organic phase separated and combined with the dichloromethane extracts of the aqueous phase. The combined organic extracts were dried and the solvent was removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (70 : 30) provided a yellow solid which was recrystallized from dichloromethane/light petroleum to give the *aniline* (0.15 g, 25%) as colourless needles, mp 46–47°C (Found: 145.0886. $C_{10}H_{11}N$ requires 145.0891). ν_{max} (CH_2Cl_2)/cm^{-1} 3405, 3300, 1605, 1500. δ_H 7.03 (2H, d, *J* 8.5, ArH), 6.62 (2H, d, *J* 8.5, ArH), 3.91 (2H, d, *J* 2.4 Hz, CH_2), 3.74 [1H, br s (exchanges with D_2O) NH], 2.25 (3H, s, Me), 2.20 (1H, t, *J* 2.4 Hz, alkyne H). *m/z* 145 (100%, M), 144 (55), 130 (52), 106 (50), 91 (24).

Also obtained from this reaction was the dialkyne N,N-*dipropargyl-4-methylaniline* (20 mg, 3%) as an orange oil (Found: 183.1042. $C_{13}H_{13}N$ requires 183.1048). ν_{max} ($CDCl_3$)/cm^{-1} 3300, 1610, 1505. δ_H 7.10 (2H, d, *J* 8.7, ArH), 6.89 (2H, d, *J* 8.7, ArH), 4.08 (4H, d, *J* 2.4, CH_2), 2.28 (3H, s, Me), 2.24 (2H, t, *J* 2.4, alkyne H). *m/z* 183 (100%, M), 168 (24), 167 (30), 144 (33), 143 (29), 142 (28).

6-Methylquinoline **21** was obtained in the following way. A mixture of 4-methyl-*N*-propargylaniline (0.10 g, 0.69 mmol) and cuprous chloride (70 mg, 0.69 mmol) in toluene (5 mL) was refluxed under an atmosphere of nitrogen for 30 min. The reaction mixture was cooled, diluted with dichloromethane (5 mL), and extracted with hydrochloric acid (10%, 3 × 10 mL). The aqueous extracts were combined and EDTA (0.25 g, 0.7 mmol) was added with stirring. The resulting mixture was basified to pH 12 with solid sodium hydroxide and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried and the solvent was removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (70 : 30) gave the *quinoline* (38 mg, 38%) as a light-sensitive orange oil, whose ^{1}H NMR spectrum was identical to that published.[12] ν_{max} (CH_2Cl_2)/cm^{-1} 1630, 1600, 1575, 1500. δ_H 8.89 (1H, m, ArH), 8.03 (2H, m, ArH), 7.53 (2H, m, ArH), 7.34 (1H, br s, ArH), 2.52 (3H, s, Me). *m/z* 143 (100%, M), 142 (46), 120 (7), 115 (16).

1,1-Dimethyl-3-trimethylsilyl-2-propynylamine **23** was obtained in the following way. 1,1-Dimethylpropargylamine (1.0 g, 12.05 mmol) in tetrahydrofuran (15 mL) was cooled to −78°C, and butyllithium (2.0 M, 6.62 mL, 13.25 mmol) was added slowly. After 30 min chlorotrimethylsilane (1.44 g, 13.25 mmol) was added and the mixture was allowed to warm to room temperature and then stirred overnight. Water (5 mL) was added and the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (15 mL), dried, the solvent was removed under reduced pressure, and the residue was distilled to give the *amine* as a colourless liquid (1.56 g, 84%), bp 67–69°/24 mm (Found: 155.1147. $C_8H_{17}NSi$ requires 155.1130). ν_{max} (film)/cm^{-1} 3370, 3300, 2160. δ_H 1.95 (2H, br s, NH_2), 1.42 (6H, s, CMe), 0.18 (9H, s, SiMe). *m/z* 155 (5%, M), 140 (100).

2-Chloro-4-(1,1-dimethyl-3-trimethylsilyl-2-propyn-1-ylamino)-pyrimidine **22** and *4-chloro-2-(1,1-dimethyl-3-trimethylsilyl-2-propyn-1-ylamino)pyrimidine* were obtained in the following way. 2,4-Dichloropyrimidine (0.123 g, 0.823 mmol), the amine **23**, and triethylamine (0.10 g, 0.99 mmol) were heated in dimethylformamide (5 mL) at 90°C for 5 h. Solvent was removed from the cooled solution under reduced pressure. The residue was dissolved in dichloromethane (10 mL), washed with sodium hydroxide solution (1 M, 2 × 10 mL), dried, and the solvent removed. The residue was chromatographed (dichloromethane/methanol, 98 : 2) to afford a yellow solid that contained both regioisomers in a ratio of 9 : 1. Fractional crystallization (ethanol/water) gave the *major isomer* **22** as colourless prisms (0.174 g, 79%), mp 89–90°C (Found: C 54.3, H 6.6, N 15.7; M 267.0966. $C_{12}H_{18}ClN_3Si$ requires C 53.8, H 6.7, N 15.7%; M 267.0959). ν_{max} (Nujol)/cm^{-1} 3272, 2164, 1674, 1600. δ_H 8.13 (1H, d, *J* 6.0, ArH), 6.82 (1H, d, *J* 6.0, ArH), 5.42 (1H, br s, NH), 1.62 (6H, s, CMe), 0.15 (9H, s, SiMe). *m/z* 267/269 (70%, M), 252/254 (100), 232 (40). The ^{1}H NMR spectrum of the minor product was obtained from the spectrum of the mother liquor material, by subtraction. δ_H 7.99 (1H, d, *J* 6.0, ArH), 6.29 (1H, d, *J* 6.0, ArH), 5.40 (1H, br s, NH), 1.46 (6H, s, CMe), 0.12 (9H, br s, SiMe).

2-Chloro-4-(1,1-dimethyl-2-propyn-1-ylamino)pyrimidine **24** was obtained in the following way. Tetrabutylammonium fluoride (1 M, 0.43 mL, 0.43 mmol) was added to a solution of **22** (108 mg, 0.40 mmol) in tetrahydrofuran (10 mL) and the mixture was stirred at room temperature overnight. Dichloromethane (10 mL) was added and the solution was extracted with water. The combined organic extracts were dried and the solvent was removed to give a yellow solid that was recrystallized from ethanol/water to give the *amine* as colourless needles (61 mg, 77%), mp 90–91°C (Found: C 55.0, H 5.2, N 21.8; M − H 194.0490. $C_9H_{10}ClN_3$ requires C 55.2, H 5.2, N 21.5%; M − H 194.0485). ν_{max} (CH_2Cl_2)/cm^{-1} 3292, 3128, 1651, 1588, 1500. δ_H 8.11 (1H, d, *J* 6.0, ArH), 6.75 (1H, d, *J* 6.0), 5.42 (1H, br s, NH), 2.43 (1H, s, alkyne H), 1.63 (6H, s, CMe). *m/z* 194/196 (96%, M − H), 180/182 (100), 160 (38).

2-Chloro-4-(1,1-dimethyl-2-propen-1-ylamino)pyrimidine **25** was obtained in the following way. The alkyne **24** (195 mg) in ether (10 mL) was stirred with a Lindlar catalyst (20 mg) under an atmosphere of hydrogen until 1.1 mmol of hydrogen had been absorbed. After the usual workup, the solution was filtered through Celite and the solvent evaporated to yield a yellow solid which was recrystallized from ethanol/water to yield the *alkene* as colourless needles (178 mg, 90%), mp 84.5–85.5°C (Found: C 54.8, H 6.1, N 21.6; M 197.0735. $C_9H_{12}ClN_3$ requires C 54.7, H 6.1, N 21.2%; M 197.0720). ν_{max} (CH_2Cl_2)/cm^{-1} 3298, 1620. δ_H 8.00 (1H, d, *J* 6.0, ArH), 6.39 (1H, d, *J* 6.0, ArH), 5.95 (1H, dd, J_{cis} 10, J_{trans} 17, C*H*=CH_2), 5.51 (1H, br s, NH), 5.21 (1H, d, J_{cis} 10, CH=CH_2), 5.20 (1H, d, J_{trans} 17, CH=CH_2), 1.46 (6H, s, CMe). *m/z* 197/199 (23%, M), 182/184 (100), 162 (14).

5-Bromo-2-chloro-4-(1,1-dimethyl-2-propyn-1-ylamino)pyrimidine **26** and *5-bromo-4-chloro-2-(1,1-dimethyl-2-propyn-1-ylamino)pyrimidine* were obtained in the following way. 5-Bromo-2,4-dichloropyrimidine[13] (0.572 g, 2.5 mmol), 1,1-dimethylpropargylamine (0.32 g, 3.8 mmol), and triethylamine (0.38 g, 3.8 mmol) were heated in dimethylformamide (10 mL) at 90°C for 5 h. The solvent was evaporated from the cooled solution and the residue was dissolved in dichloromethane, washed with sodium hydroxide solution (1 M, 2 × 15 mL), dried, and the solvent evaporated. The yellow oil thus obtained was chromatographed (dichloromethane) to give a solid which was recrystallized from ethanol/water to give the *major isomer* **26** as colourless needles (0.523 g, 76%), mp 81–81.5°C (Found: C 39.5, H 3.4, N 15.4; M 272.9679. $C_9H_9BrClN_3$ requires C 39.4, H 3.3, N 15.3%; M 272.9670). ν_{max} (Nujol)/cm^{-1} 3420, 3216. 2158, 1640, 1600. δ_H 8.17 (1H, s, ArH), 5.61 (1H, br s, NH), 2.39 (1H, s, alkyne H), 1.80 (6H, s, Me). *m/z* 273/275/277 (100%, M), 258/260/262 (92).

The ^{1}H NMR spectrum of the minor isomer also present was determined from a spectrum of the mother liquor material, by subtraction. δ_H 8.38 (1H, s, ArH), 5.48 (1H, br s, NH), 2.31 (1H, s, alkyne H), 1.72 (6H, s, Me).

5-Bromo-2-chloro-4-(1,1-dimethyl-2-propen-1-ylamino)pyrimidine **27** was obtained in the following way. The alkyne **26** was reduced as described for the alkyne **24** to give the *alkene* as colourless needles (91%) after recrystallization from ethanol/water, mp 57–58°C (Found: C 39.0, H 4.0, N 15.2. $C_9H_{11}BrClN_3$ requires C 39.1, H 4.0, N 15.2%). ν_{max} (Nujol)/cm^{-1} 3316, 1582. δ_H 8.11 (1H, s, ArH), 6.12 (1H, d, J_{cis} 10, J_{trans} 17, C*H*=CH_2), 5.56 (1H, br s, NH), 5.18 (1H, d, J_{trans} 17, CH=CH_2), 5.12 (1H, d, J_{cis} 10, CH=CH_2), 1.60 (6H, s, Me). *m/z* 275/277/279 (38%, M), 260/262/264 (100).

*2-Chloro-6,6-dimethyl-5-methylene-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine* **28** was obtained in the following way. The alkene **27** (20 mg, 0.075 mmol), triethylamine (0.22 g, 2.2 mmol), palladium acetate (2 mg, 0.0075 mmol), and tri-*o*-tolylphosphine (5 mg, 0.015 mmol) were heated and stirred at 100°C for 16 h in a sealed tube. The mixture was diluted with water and extracted with ether (3 × 15 mL); the organic extracts were dried and evaporated. The residue was chromatographed, using hexane/dichloromethane, to afford the *title compound* as a colourless oil (10 mg, 70%) (Found: C 55.4, H 5.1, N 21.2. $C_9H_{10}Cl_3$ requires C 55.3, H 5.2, N 21.5%). ν_{max} (CH_2Cl_2)/cm^{-1} 3270, 1622. δ_H 8.09 (1H, s, ArH), 6.65 (1H, br s, NH), 5.54 (1H, s, C=CH_2), 5.13 (1H, s, C=CH_2), 1.44 (6H, s, Me). *m/z* 195/197 (24%, M), 180/182 (100).

*2-Chloro-7,7-dimethyl-6-phenylselanyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine* **29** was obtained in the following way. Phenylselanyl bromide (0.373 g, 1.58 mmol) in dry dichloromethane (5 mL) was added dropwise to a mixture of the amine **28** (0.402 g, 1.51 mmol), anhydrous potassium carbonate (2.08 g, 15.1 mmol), and dry silica gel (0.40 g, Merck 60, 230–400 mesh) in dry dichloromethane (15 mL) over 15 min and the mixture was stirred at room temperature, in the dark, for 12 h. The reaction mixture was filtered through Celite and the residue washed with dichloromethane (3 × 25 mL). The filtrate was washed with water (2 × 20 mL), then saturated sodium bicarbonate solution (2 × 20 mL), dried, and evaporated to yield an oil that was chromatographed sequentially on two flash columns. The first column (methanol/dichloromethane, 5 : 95) removed selenium-containing byproducts, while the second, using chloroform/acetone (98 : 2), yielded the *title compound* as a pale yellow oil (0.315 g, 66%) (Found: 353.0198. $C_{15}H_{16}{}^{35}ClN_3{}^{77}Se$ requires 353.0187). ν_{max} (CH_2Cl_2)/cm^{-1} 3275, 1600, 1500. δ_H 7.48 (2H, m, ArSe), 7.30 (1H, s, ArH), 7.20 (3H, m, ArSe), 4.34 (1H, br s, NH), 4.27 (1H, dd, J_{ax} 2, J_{bx} 8, CH_xCH_aH$_b$), 3.21 (1H, dd, J_{ab} 13, J_{bx} 8, CH$_x$CH$_a$H$_b$), 3.08 (1H, dd, J_{ax} 2, J_{ab} 13,

$CH_xCH_aH_b$), 1.46 (3H, s, Me), 1.24 (3H, s, Me). *m/z* 351/353/355/357 (65%, M), 276/278/280/282 (100).

*2-Chloro-7,7-dimethyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine* **30** was obtained in the following way. The selenide **29** (20 mg, 0.06 mmol) was dissolved in tetrahydrofuran (2 mL), butyllithium (2 M, 60 μL, 0.12 mmol) was added to the solution at room temperature, and the mixture was stirred for 30 min. Water was then added, the mixture was stirred for 15 min, and then extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (2 × 10 mL), dried, and the solvent was removed under reduced pressure. The residue was chromatographed (dichloromethane/methanol) to yield the *reduction product* as a pale yellow oil (6 mg, 54%) (Found: 197.0706. $C_9H_{12}ClN_3$ requires 197.0720). ν_{max} (CH_2Cl_2)/cm^{-1} 3266. δ_H 7.36 (1H, s, ArH), 5.44 (1H, br s, NH), 3.58 (2H, t, *J* 7.0, CH_2), 2.85 (2H, t, *J* 7.0, CH_2), 1.29 (6H, s, Me). *m/z* 197/199 (28%, M), 182/184 (100).

*2-Chloro-7,7-dimethyl-7,8-dihydropyrido[2,3-*d*]pyrimidine* **31** was obtained in the following way. A solution of sodium periodate (50 mg, 0.22 mmol) in water (1 mL) was added dropwise to a solution of the selenide **29** (35 mg, 0.1 mmol) in methanol (3.5 mL) and water (1.5 mL) at 0°C. The mixture was allowed to warm to room temperature and then stirred overnight. The mixture was filtered, the precipitate washed with methanol (2 × 3 mL), and the filtrate concentrated. Dichloromethane was added to the residue, and the solution was washed with water (2 × 5 mL), then dried, and the solvent evaporated. The residue was chromatographed (methanol/dichloromethane, 2 : 98) to afford the *title compound* as a colourless oil (3.4 mg, 18%) (Found: 195.0571. $C_9H_{10}ClN_3$ requires 195.0563). ν_{max} (CH_2Cl_2)/cm^{-1} 3281, 1620. δ_H [$(CD_3)_2O$] 7.55 (1H, s, ArH), 7.04 (1H, d, *J* 8.0, C*H*=CH), 5.22 (1H, d, *J* 8.0, CH=C*H*), 2.93 (1H, br s, NH), 1.49 (6H, s, Me). *m/z* 195/197 (76%, M), 180/182 (100).

This compound was also made (17%) using hydrogen peroxide (30%) as the oxidant.

Acknowledgments

M.A.H. thanks the University of Adelaide for the award of a Postgraduate Scholarship. N.M.W. acknowledges, with gratitude, the assistance of an Australian Postgraduate Research Award (Priority).

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