One-pot synthesis of tetrasubstituted pyrazoles—proof of regiochemistry

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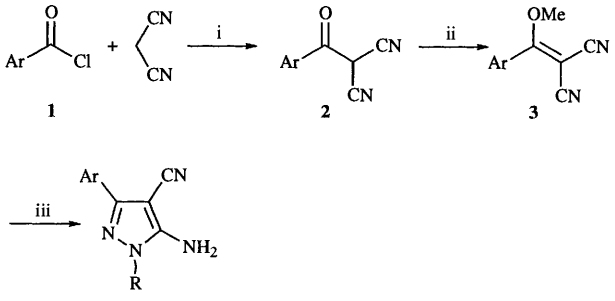
1-Alkyl-5-amino-3-aryl-4-cyanopyrazoles, useful intermediates for fused heterocyclic systems, are synthesised by a one-pot three-step procedure from acid chlorides, malononitrile and alkylhydrazines. The regiochemistry of the hydrazine incorporation was proved in each case by X-ray crystallography and NMR spectroscopy.

Pyrazoles and their derivatives are widely used as pharmaceuticals and agrochemicals, the earliest example, antipyrine, dating from 1884.[1] Since then the chemistry of pyrazoles has received much attention and many methods for their synthesis have been developed. There is significant interest in the preparation of 5-amino-4-cyanopyrazoles and pyrazolin-5-one-4-carboxylates, with a wide array of groups at N-1, as these are used as intermediates for fused heterocyclic systems. Yet in most cases authors give no proof for the regiochemistry of the cyclisation. In 1895 Claisen and Haase[2] described a synthesis of ethyl 1-phenylpyrazolin-5-one-4-carboxylates from ethyl ethoxymethylidenemalonate and phenylhydrazine and provided definitive proof for the regiochemistry. A preparation of ethyl 1-phenylpyrazolin-3-one-4-carboxylate using acetylphenylhydrazine was published in 1907.[3] This work is often quoted as evidence for the general selectivity observed in the synthesis of 1-alkyl- and 1-phenyl-5-amino-4-cyano-pyrazoles and pyrazolin-5-one-4-carboxylates from specific hydrazines and ethoxymethylidene malonic ester, ethoxymethylidenemalononitrile, or their derivatives. There are a few examples where it was stated that the reactions are not always regioselective.[4] One of these was quoted as proof of the selectivity,[5] and since then it has been accepted that evidence for the selectivity is no longer required.[6] When the first synthesis of 5-amino-4-cyano-1-alkylpyrazoles was described[7] the regiochemistry was assumed always to be the same as that observed by Claisen and Haase, which was not necessarily true. We therefore felt that it was necessary to provide proof of the regiochemistry of each reaction investigated.

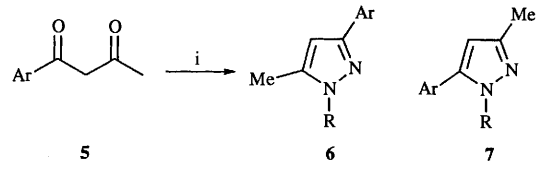
The aim was to develop a method which could readily provide large quantities of pyrazoles, particularly sterically congested ones, as building blocks for fused heterocyclic systems. In general the synthesis of 5-amino-4-cyanopyrazoles involves three steps,[7] some using toxic chemicals. In the case of 5-amino-3-(*p*-chlorophenyl)-4-cyano-1-methylpyrazole[8] (location of the methyl group unproven) the intermediate **3f** was prepared using dimethyl sulfate as co-solvent. Starting with readily available benzoyl chlorides **1**, malononitrile and alkylhydrazine hydrochlorides we could prepare **4a–g** using a one-pot procedure without halogenated solvents nor with a large excess of reagents at any stage (Scheme 1). Furthermore, sodium hydride could be used as a dispersion in paraffin oil and any unreacted dimethyl sulfate was destroyed before work-up. The products were purified by recrystallisation or filtration over a pad of silica. It was thus possible to prepare multigram quantities of crystalline material in a short time, and the yields (*e.g.* **4f** 58%; **4g** 51%) were comparable to those of the normal three-step procedure (**4f** 50%; **4g** 39%).

In preliminary experiments, *tert*-butylhydrazine was treated with the β-diketone **5a** under different conditions (see Experimental) to give always the 5-aryl isomer **7a**. Diketone **5b** also gave only isomer **7b**; in both cases the other regioisomer (**6a** or **6b**) was not observed. However, cyclohexylhydrazine[9] gave, in the same reaction, a mixture of both regioisomers **6c** and **7c** (Scheme 2). To probe whether a similar lack of selectivity would be observed in the one-pot reaction (Scheme 1), the *N*-cyclohexylpyrazole **4g** was prepared by this method; no other regioisomer was detectable. This points to high selectivity in the one-pot procedure.



a Ar = Ph, R = Bu^t
b Ar = *p*-MeOC$_6$H$_4$, R = Bu^t
c Ar = *p*-O$_2$NC$_6$H$_4$, R = Bu^t
d Ar = *o*-ClC$_6$H$_4$, R = Bu^t
e Ar = *m*-ClC$_6$H$_4$, R = Bu^t
f Ar = *p*-ClC$_6$H$_4$, R = Bu^t
g Ar = *p*-ClC$_6$H$_4$, R = cyclohexyl

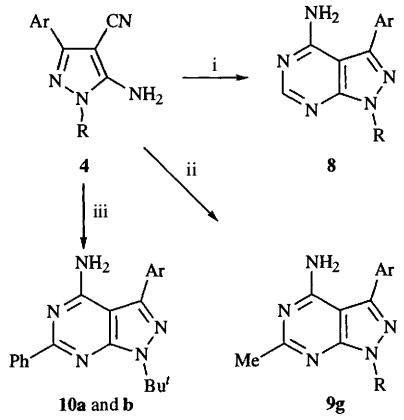
Scheme 1 *Reagents and conditions:* i, malononitrile, NaH, THF, **1** 5–10 °C, 1 h, room temp.; ii, dimethylsulfate, reflux; iii, triethylamine, alkylhydrazine hydrochloride, reflux



a Ar = Ph, R = Bu^t
b Ar = *p*-ClC$_6$H$_4$, R = Bu^t
c Ar = Ph, R = cyclohexyl

Scheme 2 *Reagents and conditions:* i, alkylhydrazine hydrochloride, triethylamine, EtOH, reflux

The aminonitriles **4a–e** and **g** were readily converted with formamide[10] into pyrazolopyrimidines **8a–e** and **g** (Scheme 3). The use of acetamide in order to obtain a methyl group at position 6 failed. The following reactions were attempted: with thioacetamide,[11] acetamidine,[12] ethyl acetimidate,[13] benzyl



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e Ar = *m*-ClC$_6$H$_4$, R = Bu^t
f Ar = *p*-ClC$_6$H$_4$, R = cyclohexyl

Scheme 3 *Reagents and conditions:* i, formamide, reflux; ii, methanolic ammonia, acetonitrile, autoclave, 190 °C; iii, methanolic ammonia, benzonitrile, autoclave, 200 °C; or NaOEt, benzonitrile, EtOH, reflux

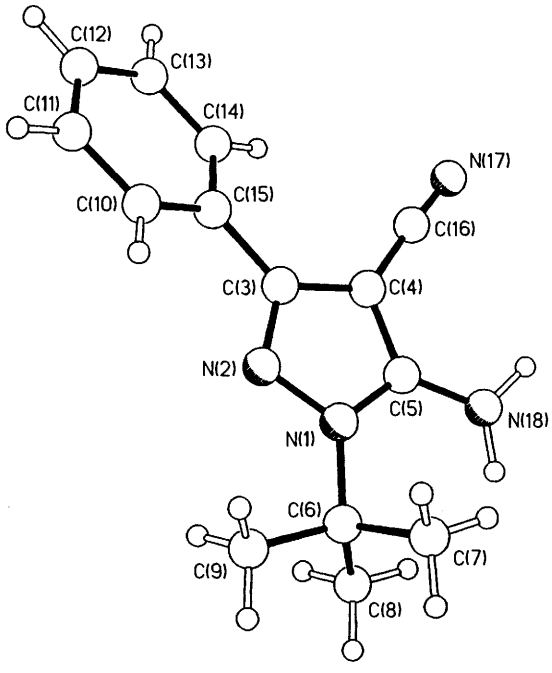

Fig. 1 The molecular structure of **4a**

thioacetimidate,[14] triethyl orthoacetate and subsequent treatment with ammonia,†[,15] acetonitrile in the presence of sodium ethoxide,[16] and with acetonitrile in methanolic ammonia in an autoclave.[16] All were unsuccessful when R was *tert*-butyl. When **4g** (R = cyclohexyl) was treated with acetonitrile–methanolic ammonia under pressure at high temperatures, the pyrazolopyrimidine **9g** could be isolated in 60% yield. This presumably results from the 5-amino group in **4g** being less hindered than the *tert*-butyl compound, but even with R = *tert*-butyl it was possible to introduce a phenyl substituent at position 6. Thus with benzonitrile–sodium ethoxide or benzonitrile–methanolic ammonia the pyrazolopyrimidines **10a** and **b** were prepared from pyrazoles **4a** and **b**. This may reflect the greater reactivity of the ethyl benzimidate and benzamidine that are the presumed intermediates.

† Instead, 5-acetiminoethyl-1-*tert*-butyl-3-(*p*-chlorophenyl)-4-cyanopyrazole was obtained as an oil (Found: M$^+$, 344.14124. $C_{18}H_{21}ClN_4O$ requires *M*, 344.14039); δ_H(270 MHz; [$^2H_6$]DMSO) 1.44 (3 H, t, ^3J 6.9, OCH_2CH_3), 1.57 (9 H, s, Bu^t), 2.10 (3 H, s, Me), 4.34 (2 H, q, ^3J 6.9, OCH_2CH_3), 7.57 (2 H, m, 3′-H, 5′-H) and 7.86 (2 H, m, 2′-H, 6′-H); δ_C(250 MHz; $CDCl_3$) 14.2 (1 C, OCH_2CH_3), 18.0 (1 C, Me), 29.1 [3 C, $C(CH_3)_3$], 61.2 [1 C, $C(CH_3)_3$], 63.4 (1 C, OCH_2CH_3), 80.6 (1 C, C-4), 115.5 (1 C, CN), 127.4 (2 C, C-3′, C-5′), 128.9 (2 C, C-2′, C-6′), 130.3 (1 C, C-1′), 135.6 (1 C, C-4′), 147.4 (1 C, C-3), 152.7 (1 C, C-5) and 166.3 (1 *C*NOEt).

Table 1 Selected bond lengths (Å) and aryl/pyrazole twist angles (°) in **4a**, **b**, **e** and **f**

	4a	**4b**	**4e**	**4f**
N(1)–N(2)	1.378(2)	1.381(2)	1.369(6)	1.374(6)
N(2)–C(3)	1.321(3)	1.323(2)	1.325(7)	1.326(5)
C(3)–C(4)	1.419(3)	1.416(2)	1.410(8)	1.418(6)
C(4)–C(5)	1.386(3)	1.385(3)	1.380(8)	1.373(7)
C(5)–N(1)	1.344(3)	1.344(2)	1.352(7)	1.339(5)
N(1)–C(*tert*-butyl)	1.496(3)	1.497(2)	1.494(7)	1.510(6)
C(3)–C(aryl)	1.467(3)	1.476(3)	1.446(10)	1.457(7)
C(4)–C(cyano)	1.415(3)	1.420(2)	1.423(8)	1.428(6)
C(5)–N(amino)	1.361(3)	1.375(3)	1.358(8)	1.382(7)
Twist angle between aryl and pyrazole rings	24	11	0	13

Regiochemistry of the *N*-alkyl group incorporation

The intermediates **3a–f** can react with the alkylhydrazines in four different ways to yield two different regioisomers, **4a–g** or the corresponding 1-alkyl-3-amino-5-aryl-4-cyanopyrazoles. We therefore had to assign the structures of **4a–g** on firm evidence. For pyrazole **4g** the structure was established by NOE experiments. For pyrazoles **4a–f** this was not possible. The *tert*-butyl group is, even in the confirmed regiochemistry, too far away from the protons of the amino group to make a reliable NOE experiment possible. Furthermore only one out of nine protons of the *tert*-butyl group is adjacent to either of the other substituents at any given time. The structures of **4a**,**b**,**e** and **f** were therefore determined by X-ray crystallography.

The X-ray structural studies of **4a**,**b**,**e** and **f** establish a consistent 1-alkyl-3-aryl-4-cyano-5-amino substitution regiochemistry. Fig. 1 shows a representative view of the conformation observed in all four structures, the pyrazole ring in each case being planar to within 0.006 Å. The immediate ring substituents in all four structures lie close to this plane with the exception of the quaternary *tert*-butyl carbon atom in **4b** and **4f**, where this atom lies 0.24 and 0.19 Å out of plane respectively, reflecting differing degrees of pyramidalisation at N(1) (which lies 0.09 and 0.07 Å out of the plane of its substituents in **4b** and **4f** respectively). The only major conformational differences are in the relative twists of the aryl ring with respect to the pyrazole moiety, which range from 0° in **4e** (where the molecule is constrained, with the exception of one of the *tert*-butyl methyl carbon atoms, to lie on a crystallographic mirror plane) to 24° in **4a**.

The pattern of bonding within the pyrazole ring in all four structures is, within statistical significance, the same, indicating in each case a marked degree of delocalisation (Table 1). The remaining bond lengths and angles are normal.

Inspection of the packing of the molecules of **4a**,**b**,**e** and **f** reveals two distinct patterns of N–H · · · N hydrogen bonding, each of which involve one of the amino hydrogen atoms and the cyano nitrogen atom. In **4a** and **4e** the molecules are linked (N · · · N distances 3.10 and 3.06 Å respectively) to form chains that extend along the crystallographic *b* direction [Fig. 2(*a*)] whilst in **4b** and **4f** centrosymmetrically related pairs of molecules are linked (N · · · N distances 3.10 and 3.09 Å respectively) to form hydrogen-bonded dimer pairs, as shown in Fig. 2(*b*). In the latter two structures the molecules form polar stacks with the pyrazole ring of one molecule overlapping the phenyl ring of the next, the rings being approximately parallel

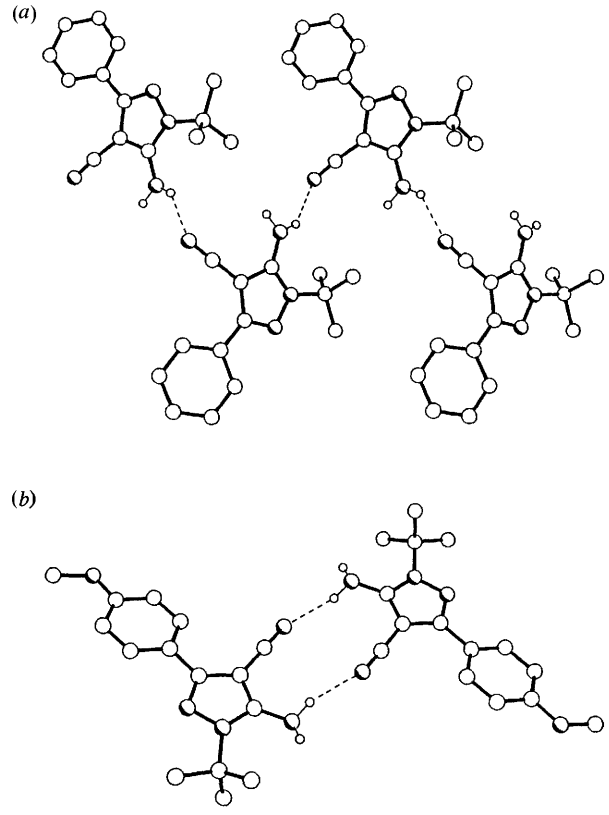

Fig. 2 (*a*) Part of one of the N–H · · · N hydrogen-bonded chains of molecules in **4a** (an almost identical pattern is present for **4e**). Hydrogen bonding geometries; N · · · N, H · · · N distances (Å), N–H · · · N angles (°); **4a**, 3.10, 2.26, 146; **4e**, 3.06, 2.22, 145. (*b*) The hydrogen-bonded dimer pair arrangement present in **4b** and **4f**. Hydrogen bonding geometries; N · · · N, H · · · N distances (Å), N–H · · · N angles (°); **4b**, 3.10, 2.17, 164; **4f**, 3.09, 2.15, 168.

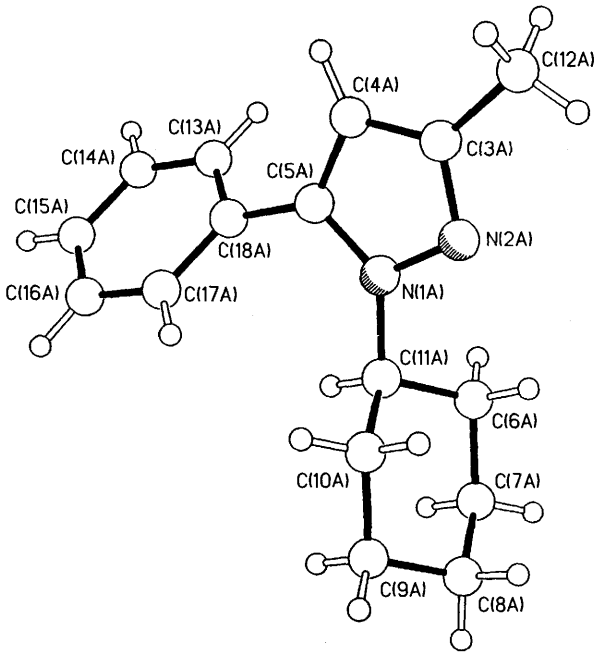

Fig. 3 The molecular structure of **7c** showing one of the four crystallographically independent molecules

(inclined by 11° in **4b** and 13° in **4f**) and with mean interplanar separations of 3.48 and 3.54 Å in **4b** and **4f** respectively. There are no analogous stacking motifs in the structures of **4a** and **4e**.

The X-ray analysis of **7c** shows the cyclohexyl substitution on the pyrazole ring to have occurred on the nitrogen atom *ortho* to the phenyl group (Fig. 3). Compound **7c** crystallises with four crystallographically independent molecules in the asymmetric

Table 2 Selected bond lengths (Å) and aryl/pyrazole twist angles (°) in the four crystallographically independent molecules **A**, **B**, **C** and **D** in **7c**

	A	B	C	D
N(1)–N(2)	1.362(3)	1.369(3)	1.361(3)	1.358(3)
N(2)–C(3)	1.333(3)	1.330(3)	1.339(3)	1.326(3)
C(3)–C(4)	1.391(4)	1.397(4)	1.395(4)	1.389(4)
C(4)–C(5)	1.373(3)	1.370(3)	1.375(3)	1.366(3)
C(5)–N(1)	1.363(3)	1.359(3)	1.348(3)	1.352(3)
N(1)–C(cyclohexyl)	1.465(3)	1.458(3)	1.471(3)	1.460(3)
C(3)–C(methyl)	1.496(4)	1.495(4)	1.492(4)	1.498(4)
C(5)–C(phenyl)	1.469(3)	1.473(4)	1.474(3)	1.484(3)
Twist angle between aryl and pyrazole rings	51	64	55	76

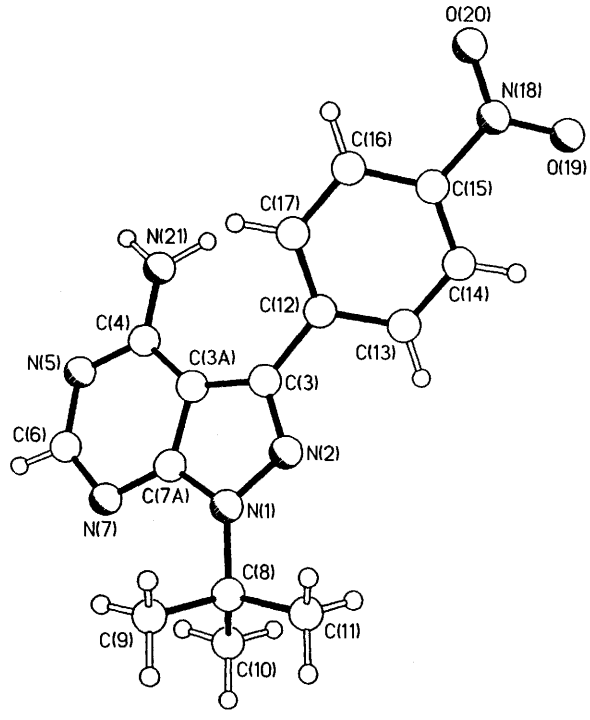

Fig. 4 The molecular structure of **8c**

unit. The bond lengths and angles within the pyrazole ring do not show any evidence for pronounced bond ordering, the pattern in all four independent molecules indicating effective delocalisation with only the N(2)–C(3) bonds being significantly shorter than the rest (Table 2). In all four independent molecules the respective orientations of the pyrazole and cyclohexyl rings are essentially the same, there being a *trans* relationship between the N–N bond of the pyrazole and the tertiary C–H bond of the cyclohexyl. The phenyl ring is twisted by varying degrees, 51–76°, with respect to the pyrazole rings in the four independent molecules. In the four different molecules the pyrazole ring is essentially planar with deviations in the range 0.001 to 0.006 Å from planarity. All four molecules exhibit varying degrees of pyramidalisation at the N(1) centre with the nitrogen atom lying between 0.012 and 0.044 Å out of the plane of its substituents. There are no significant intermolecular packing interactions.

The X-ray analyses of **8c** and **8e** (Ar = *p*-$O_2NC_6H_4$ or *m*-ClC_6H_4, respectively, R = *tert*-butyl) establish the 1-alkyl-3-aryl substitution pattern in both instances, and hence the 1,3-regiochemistry of the precursors **4c** and **4e**—see Fig. 4, which shows the structure of **8c**. The unlikely shift of the *tert*-butyl group during the formation of **8c** can be ruled out since we have shown that the conversion of **4e** to **8e** takes place without this rearrangement. For both **8c** and **8e**, inspection of the pattern of bonding in the fused pyrazole/pyrimidine unit reveals a marked

Table 3 Selected bond lengths (Å) and aryl/fused ring twist angles (°) in **8c** and **8e**

	8c	8e
N(1)–N(2)	1.370(3)	1.344(7)
N(2)–C(3)	1.313(3)	1.322(7)
C(3)–C(3A)	1.429(3)	1.433(8)
C(3A)–C(4)	1.407(3)	1.426(8)
C(4)–N(5)	1.350(3)	1.332(8)
N(5)–C(6)	1.343(4)	1.355(8)
C(6)–N(7)	1.312(3)	1.327(8)
N(7)–C(7A)	1.354(3)	1.350(8)
C(7A)–N(1)	1.367(3)	1.373(8)
C(7A)–C(3A)	1.387(4)	1.377(7)
N(1)–C(*tert*-butyl)	1.481(4)	1.502(7)
C(3)–C(aryl)	1.477(4)	1.461(8)
C(4)–N(amino)	1.329(4)	1.347(7)
Twist angle between aryl and fused rings	41	35

delocalisation of the π-bonding pattern with only the N(2)–C(3) and the C(6)–N(7) bonds exhibiting any significant double bond character and C(3)–C(3A) a pronounced single bond nature (Table 3). This ring system is planar to within 0.037 Å in **8c** and 0.051 Å in **8e**, [for C(4) in both structures] with the amino nitrogen atom having the largest departure from this plane of any of the three immediate substituents; 0.12 Å in **8c** and 0.15 Å in **8e**. The aryl ring is rotated out of the plane of the pyrazole by 41 and 35° for **8c** and **8e** respectively.

Inspection of the packing of the molecules reveals a very similar pattern of extended hydrogen bonding for both structures. Centrosymmetrically related molecules are linked *via* pairs of N–H • • • N hydrogen bonds between one of the C(4) amino N–H hydrogen atoms in one molecule and the pyrimidine N(5) nitrogen atom in another and *vice versa* (N • • • N 3.00 and 2.97 Å in **8c** and **8e** respectively). In **8c** these pairs are in turn linked across an independent symmetry centre *via* weak N–H • • • O hydrogen-bonds involving the other amino hydrogen atom and one of the nitro oxygen atoms [N • • • O 3.07 Å] to form ribbons that extend in the crystallographic *c* direction [Fig. 5(*a*)]. In **8e**, this secondary hydrogen bonding pattern is reproduced involving again the same amino nitrogen atom as the donor N–H group, but with the substituted aryl chlorine atom as the acceptor instead of the nitro oxygen atom (N • • • Cl 3.34 Å) [Fig. 5(*b*)].

In **8c**, the secondary N–H • • • O hydrogen-bonding is supplemented by a π-stacking interaction between the two *para*-nitrophenyl substituents (interplanar separation 3.37 Å), the two ring systems being offset such that the nitrogen atom of one molecule is positioned almost directly over the phenyl ring of the next (N • • • ring centroid distance, 3.43 Å) and *vice versa*. In **8e** there is an analogous stacking motif, although with approximately 50% ring–ring overlap. The interplanar separation, however, is markedly increased to 3.90 Å.

Pyrazole **4d** is an unstable oil and it was therefore converted into **8d** for characterisation. The ^{1}H NMR shift of the *tert*-butyl group of **8a–c** and **e** is δ 1.73 ± 0.03, the ^{13}C NMR shift of the quaternary carbon of the *tert*-butyl group is δ 59.7 ± 0.3, and that of the methyl groups is δ 28.7 ± 0.1. The corresponding signals of **8d** are all within these limits supporting the structural assignment. The regiochemistry of **7a–c** and of **6c** was established by NOE experiments and, in the case of **7c**, also by X-ray crystallography (see above).

Experimental

Elemental microanalyses were performed in the departmental microanalytical laboratory. NMR spectra were recorded on Bruker AM-500 (500 MHz, ^{1}H NMR; 124.6 MHz, ^{13}C NMR),

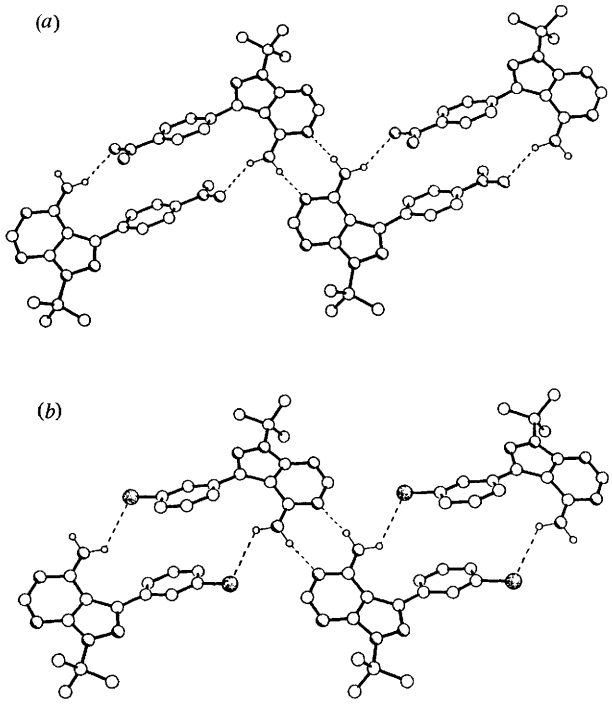

Fig. 5 (*a*) Part of one of the hydrogen-bonded ribbons present in the structure of **8c**. Hydrogen bonding geometries; N • • • N, H • • • N distances (Å), N–H • • • N angle (°), N • • • O, H • • • O distances (Å), N–H • • • O angle (°); 3.00, 2.05, 172; 3.07, 2.19, 151. (*b*) Part of one of the analogous hydrogen-bonded ribbons present in the structure of **8e**. Hydrogen bonding geometries; N • • • N, H • • • N distances (Å), N–H • • • N angle (°), N • • • Cl, H • • • Cl distances (Å), N–H • • • Cl angle (°); 2.97, 2.03, 167, 3.34, 2.69, 126.

Bruker AMX-400 (400 MHz, ^{1}H NMR; 99.7 MHz, ^{13}C NMR), JEOL GSX 270 (270 MHz, ^{1}H NMR) and Bruker WM-250 (250 MHz, ^{1}H NMR; 62.3 MHz, ^{13}C NMR) spectrometers. ^{1}H NMR spectra were referenced internally on $CHCl_3$ (δ 7.27) or DMSO (δ 2.49). ^{13}C NMR spectra were referenced on $CDCl_3$ (δ 77.5), or DMSO (δ 39.70). *J* Values are given in Hz. Mass measurements were recorded on an AE1 MS12 and VG Micromass 7070B. Chromatography was performed using Sorbsil 40–60 μm. All compounds described in this Experimental section were homogeneous on TLC.

p-Chlorobenzoylmalononitrile 2f

To malononitrile (6.61 g, 0.1 mol) in THF (100 ml) and sodium hydride (4.80 g, 0.2 mol; 80% dispersion in paraffin oil) *p*-chlorobenzoylchloride (17.50 g, 0.1 mol, 12.7 ml) was added dropwise at 5–10 °C. After warming to room temperature, hydrochloric acid (1 mol l^{-1} 250 ml) was added. The mixture was extracted with ethyl acetate (3 × 100 ml) and the organic layer was dried over $MgSO_4$. Recrystallisation from ethyl acetate gave **2f** (19.78 g, 97%), mp 181 °C (decomp.) (lit.,[17] mp 195 °C); δ_H(270 MHz; [$^2H_6$]DMSO) 4.57 (1 H, s, 3-H), 7.42 (2 H, m, 3′-H, 5′-H) and 7.57 (2 H, m, 2′-H, 6′-H).

p-Chlorophenyl(methoxy)methylidenemalononitrile 3f[8]

To sodium hydrogen carbonate (5 g) in 1,4-dioxane (12 ml) and water (2 ml), compound **2f** (1.53 g, 7.5 mmol) and dimethyl sulfate (5 ml) were added slowly. After stirring at 80–90 °C for 2.5 h, water (60 ml) was added. Extraction with *tert*-butyl methyl ether (4 × 30 ml), drying of the organic layer over Na_2SO_4 and recrystallisation from methanol gave **3f** (1.04 g, 63%), mp 119–122 °C (lit.,[8] mp 123 °C); δ_H(250 MHz; [$^2H_6$]DMSO) 3.88 (3 H, s, OMe), 7.72 (4 H, s, *p*-chlorophenyl).

5-Amino-1-*tert*-butyl-3-(*p*-chlorophenyl)-4-cyanopyrazole 4f

To compound **3f** (437 mg, 2.0 mmol) in ethanol (10 ml), *tert*-butylhydrazine hydrochloride (125 mg, 2.0 mmol) and

triethylamine (202 mg, 2.0 mmol) were added. After refluxing for 3.5 h the solvent was evaporated and water added. The solid was collected and recrystallised (ethanol–water) to give the title compound **4f** (435 mg, 79%), mp 158 °C (Found: C, 60.7; H, 5.5; N, 20.4. $C_{14}H_{15}ClN_4$ requires C, 61.2; H, 5.5; N 20.4%) (Found: M^+, 274.09811. $C_{14}H_{15}ClN_4$ requires *M*, 274.09852); δ_H(250 MHz; [$^2H_6$]DMSO) 1.56 (9 H, s, Bu^t), 6.42 (2 H, s, NH_2), 7.52 (2 H, m, 3′-H, 5′-H) and 7.78 (2 H, m, 2′-H, 6′-H); δ_C(124.6 MHz; [$^2H_6$]DMSO) 28.1 [3 C, C(*C*H$_3$)$_3$], 59.3 [1 C, *C*(CH$_3$)$_3$], 72.2 (1 C, C-4), 115.7 (1 C, CN), 127.1 (2 C, C-3′, C-5′), 128.7 (2 C, C-2′, C-6′), 130.7 (1 C, C-1′), 132.9 (1 C, C-4′), 145.3 (1 C, C-3) and 152.4 (1 C, C-5).

5-Amino-3-(*p*-chlorophenyl)-4-cyano-1-cyclohexylpyrazole 4g
To compound **3f** (437 mg, 2.0 mmol) in ethanol (10 ml), cyclohexylhydrazine hydrochloride (301 mg, 2.0 mmol) and triethylamine (202 mg, 2.0 mmol) were added. After refluxing for 2.0 h the solvent was evaporated and water added. The solid was collected and recrystallised (ethanol–water) to give title compound **4g** (370 mg, 62%), mp 175–176 °C (Found: C, 63.7; H, 5.7; N, 18.5. $C_{16}H_{17}ClN_4$ requires C, 63.9; H, 5.7; N, 18.6%); δ_H(250 MHz; [$^2H_6$]DMSO) 1.20 (4 H, br m, cyclohexyl), 1.77 (6 H, br m, cyclohexyl), 4.10 (1 H, m, NC*H*) 6.71 (2 H, s, NH_2), 7.50 (2 H, m, 3′-H, 5′-H) and 7.78 (2 H, m, 2′-H, 6′-H); δ_C(124.6 MHz; [$^2H_6$]DMSO) 24.7 (1 C, C-4″), 24.8 (2 C, C-3″, C-5″), 31.4 (2 C, C-2″, C-6″), 54.8 (1 C, NCH), 69.8 (1 C, C-4), 115.9 (1 C, CN), 127.2 (2 C, C-3′, C-5′), 128.7 (2 C, C-2′, C-6′), 130.7 (1 C, C-1′), 133.0 (1 C, C-4′), 147.2 (1 C, C-3) and 152.2 (1 C, C-5).

General procedure for the one-pot synthesis of 1-alkyl-5-amino-3-aryl-4-cyanopyrazoles 4a–g
To malononitrile (6.61 g, 0.10 mol) in THF (100 ml) sodium hydride (4.80 g, 0.20 mol; as 80% or 60% dispersion in paraffin oil) was added slowly with cooling. At 5–10 °C the acid chloride **1a–f** (0.10 mol) was added slowly and the reaction mixture was stirred at room temperature for 1 h. Dimethyl sulfate (15.13 g, 0.12 mol, 11.4 ml) was added and after 1.5–2.5 h of reflux, triethylamine (25.30 g, 0.25 mol, 35 ml) and the alkylhydrazine hydrochloride (0.10 mol) were added to the cold reaction mixture. After refluxing for 0.5–1.5 h the solvent was evaporated. If the residue was solid it was washed with water and light petroleum and then recrystallised. If the residue was an oil, water was added and extracted with ethyl acetate (3 × 150 ml). After drying the organic layer over $MgSO_4$ and evaporation the residue was adsorbed on silica gel, washed with light petroleum and purified by chromatography (silica gel; light petroleum–*tert*-butyl methyl ether, 1 : 1).

5-Amino-1-*tert*-butyl-4-cyano-3-phenylpyrazole 4a. Recrystallisation from ethanol gave **4a** (11.9 g, 50%), mp 120–121 °C (Found: C, 69.7; H, 6.8; N, 23.3. $C_{14}H_{16}N_4$ requires C, 70.0; H, 6.7; N, 23.3%); δ_H(400 MHz; [$^2H_6$]DMSO) 1.56 (9 H, s, Bu^t), 6.35 (2 H, s, NH_2), 7.36 (1 H, tt, ^4J 1.4, ^3J 7.2, 4′-H), 7.43 (2 H, m, 3′-H, 5′-H) and 7.76 (2 H, m, 2′-H, 6′-H); δ_C(99.7 MHz; [$^2H_6$]DMSO) 28.2 [3 C, C(*C*H$_3$)$_3$], 59.2 [1 C, *C*(CH$_3$)$_3$], 72.3 (1 C, C-4), 115.9 (1 C, CN), 125.7 (2 C, C-3′, C-5′), 128.5 (1 C, C-4′), 128.7 (2 C, C-2′, C-6′), 131.9 (1 C, C-1′), 146.6 (1 C, C-3) and 152.4 (1 C, C-5).

5-Amino-1-*tert*-butyl-4-cyano-3-(*p*-methoxyphenyl)pyrazole 4b. Recrystallisation from ethanol gave **4b** (12.5 g, 46%), mp 128 °C (Found: M^+, 270.14823. $C_{15}H_{18}N_4O$ requires *M*, 270.14806); δ_H(400 MHz; [$^2H_6$]DMSO) 1.55 (9 H, s, Bu^t), 3.77 (3 H, s, OC*H*$_3$) 6.98 (2 H, s, N*H*$_2$), 6.95 (2 H, m, 2′-H, 6′-H) and 7.52 (2 H, m, 3′-H, 5′-H); δ_C(99.7 MHz; [$^2H_6$]DMSO) 28.2 [3 C, C(*C*H$_3$)$_3$], 55.1 (1 C, O*C*H$_3$) 58.9 [1 C, *C*(CH$_3$)$_3$], 72.0 (1 C, C-4), 114.0 (2 C, C-3′, C-5′), 116.1 (1 C, *C*N), 124.5 (1 C, C-1′), 126.9 (2 C, C-2′, C-6′), 146.5 (1 C, C-3), 152.2 (1 C, C-5) and 159.4 (1 C, C-4′).

5-Amino-1-*tert*-butyl-4-cyano-3-(*p*-nitrophenyl)pyrazole 4c. Recrystallisation from ethanol gave **4c** (5.9 g, 21%), mp 194–196 °C (Found: M^+, 285.12409. $C_{14}H_{15}N_5O_2$ requires *M*, 285.12257); δ_H(250 MHz; [$^2H_6$]DMSO) 1.57 (9 H, s, Bu^t), 6.56 (2 H, s, NH_2), 8.00 (2 H, m, 3′-H, 5′-H) and 8.30 (2 H, m, 2′-H, 6′-H); δ_C(124.6 MHz; [$^2H_6$]DMSO) 28.0 [3 C, C(*C*H$_3$)$_3$], 59.7 [1 C, *C*(CH$_3$)$_3$], 72.6 (1 C, C-4), 115.4 (1 C, *C*N), 124.1 (2 C, C-3′, C-5′), 126.3 (2 C, C-2′, C-6′), 137.9 (1 C, C-1′), 144.3 (1 C, C-4′), 146.9 (1 C, C-3) and 152.8 (1 C, C-5).

5-Amino-1-*tert*-butyl-3-(*o*-chlorophenyl)-4-cyanopyrazole 4d. Chromatography gave **4d** (5.8 g, 21%) as an unstable oil (Found: M^+, 274.09734. $C_{14}H_{15}ClN_4$ requires *M*, 274.09852) which was immediately converted into **8d** and characterised as this derivative.

5-Amino-1-*tert*-butyl-3-(*m*-chlorophenyl)-4-cyanopyrazole 4e. Chromatography gave **4e** (10.8 g, 39%), mp 100–102 °C (Found: C, 61.3; H, 5.6; N, 20.1. $C_{14}H_{15}ClN_4$ requires C, 61.2; H, 5.5; N, 20.4%); δ_H(500 MHz; [$^2H_6$]DMSO) 1.56 (9 H, s, Bu^t), 6.41 (2 H, s, NH_2), 7.44 (1 H, ddd, ^3J 8.3, ^4J 1.7, ^4J 1.8, 4′-H), 7.48 (1 H, dd, ^3J 7.8, ^3J 7.8, 5′-H), 7.74 (1 H, ddd, ^3J 7.6, ^4J 1.8, ^4J 1.7, 6′-H) and 7.76 (1 H, dd, ^4J 1.7, ^4J 1.7, 2′-H); δ_C(124.6 MHz; [$^2H_6$]DMSO) 28.1 [3 C, C(*C*H$_3$)$_3$], 59.4 [1 C, *C*(CH$_3$)$_3$], 72.3 (1 C, C-4), 115.6 (1 C, *C*N), 124.1 (1 C, C-6′), 124.9 (1 C, C-5′), 128.3 (1 C, C-2′), 130.7 (1 C, C-4′), 133.4 (1 C, C-3′), 133.8 (1 C, C-1′), 144.9 (1 C, C-3) and 152.5 (1 C, C-5).

5-Amino-1-*tert*-butyl-3-(*p*-chlorophenyl)-4-cyanopyrazole 4f. Recrystallisation from ethanol gave **4f** (16.0 g, 58%) identical with that described above.

5-Amino-3-(*p*-chlorophenyl)-4-cyano-1-cyclohexylpyrazole 4g. The reaction was performed on a 0.05 molar scale. Recrystallisation from ethanol gave **4g** (7.61 g, 51%) identical with that described above.

General procedure for the synthesis of 1-alkyl-4-amino-3-arylpyrazolo[3,4-*d*]pyrimidines 8a–e and g
The pyrazole **4a–e** or **g** (1 g, except where noted otherwise) was refluxed in formamide (15 ml, except where noted otherwise) for 3 h. The cold reaction mixture was diluted with water and the precipitate was collected and redissolved in hot ethanol and decolourised with charcoal. The ethanol was evaporated to give the pure products.

4-Amino-1-*tert*-butyl-3-phenylpyrazolo[3,4-*d*]pyrimidine 8a. Pyrazole **4a** (2 g, 8.32 mmol) and formamide (25 ml) gave **8a** (2.18 g, 98%), mp 152–155 °C (Found: M^+, 267.147 42. $C_{15}H_{17}N_5$ requires *M*, 267.14840); δ_H(500 MHz; [$^2H_6$]DMSO) 1.74 (9 H, s, Bu^t), 6.60 (2 H, br s, NH_2), 7.46 (1 H, tt, ^4J 2.0, ^3J 7.3, 4′-H), 7.53 (2 H, t, ^3J 7.6, 3′-H, 5′-H), 7.64 (2 H, m, 2′-H, 6′-H) and 8.23 (1 H, s, 6-H); δ_C(124.6 MHz; [$^2H_6$]DMSO) 28.7 [3 C, C(*C*H$_3$)$_3$], 59.6 [1 C, *C*(CH$_3$)$_3$], 98.6 (1 C, C-3a), 128.3 (2 C, C-3′, C-5′), 128.4 (1 C, C-4′), 129.0 (2 C, C-2′, C-6′), 133.2 (1 C, C-1′), 141.6 (1 C, C-3), 153.8 (1 C, C-7a), 154.6 (1 C, C-6) and 158.2 (1 C, C-4).

4-Amino-1-*tert*-butyl-3-(*p*-methoxyphenyl)pyrazolo[3,4-*d*]pyrimidine 8b. (1.06 g, 96%), mp 161 °C (Found: M^+, 297.160 95. $C_{16}H_{19}N_5O$ requires *M*, 297.15896); δ_H(400 MHz; [$^2H_6$]-DMSO) 1.73 (9 H, s, Bu^t), 3.81 (3 H, s, OC*H*$_3$) 6.60 (2 H, br s, N*H*$_2$), 7.09 (2 H, m, 2′-H, 6′-H), 7.56 (2 H, m, 3′-H, 5′-H) and 8.21 (1 H, s, 6-H); δ_C(99.7 MHz; [$^2H_6$]DMSO) 28.8 [3 C, C(*C*H$_3$)$_3$], 55.2 (1 C, O*C*H$_3$), 60.0 [1 C, *C*(CH$_3$)$_3$], 98.6 (1 C, C-3a), 114.5 (2 C, C-3′, C-5′), 125.6 (1 C, C-1′), 129.6 (2 C, C-2′, C-6′), 141.5 (1 C, C-3), 153.8 (1 C, C-7a), 154.6 (1 C, C-6), 158.2 (1 C, C-4) and 159.5 (1 C, C-4′).

4-Amino-1-*tert*-butyl-3-(*p*-nitrophenyl)pyrazolo[3,4-*d*]pyrimidine 8c. Pyrazole **4c** (500 mg, 1.75 mmol) and formamide (6 ml) gave **8c** (380 mg, 96%), mp 222 °C (Found: C, 57.4; H, 5.0; N, 26.7. $C_{15}H_{16}N_6O_2$ requires C, 57.7; H, 5.2; N, 26.9%); δ_H(500 MHz; [$^2H_6$]DMSO) 1.75 (9 H, s, Bu^t), 7.00 (2 H, br s, NH_2), 7.90 (2 H, m, 3′-H, 5′-H), 8.26 (1 H, s, 6-H) and 8.36 (2 H, m, 2′-H, 6′-H); δ_C(124.6 MHz; [$^2H_6$]DMSO) 28.6 [3 C, C(*C*H$_3$)$_3$], 60.1 [1 C, *C*(CH$_3$)$_3$], 98.8 (1 C, C-3a), 124.1 (2 C, C-3′, C-5′), 129.4 (2 C, C-2′, C-6′), 139.6 (1 C, C-1′), 139.8 (1 C, C-3), 147.0

(1 C, C-4'), 154.3 (1 C, C-7a), 154.8 (1 C, C-6) and 158.2 (1 C, C-4).

4-Amino-1-*tert*-butyl-3-(*o*-chlorophenyl)pyrazolo[3,4-*d*]pyrimidine 8d. (340 mg, 31%), solidified oil, mp 106–111 °C (Found: M^+, 301.10747. $C_{15}H_{16}ClN_5$ requires *M*, 301.10942); δ_H(500 MHz; [$^2H_6$]DMSO) 1.73 (9 H, s, Bu^t), 6.90 (2 H, br s, NH_2), 7.46 (1 H, m, 5'-H), 7.51 (1 H, d, ^3J 8.0, 3'-H), 7.52 (1 H, m, 4'-H), 7.61 (1 H, m, 6'-H) and 8.23 (1 H, s, 6-H); δ_C(124.6 MHz; [$^2H_6$]DMSO) 28.7 [3 C, C(*C*H$_3$)$_3$], 59.8 [1 C, *C*(CH$_3$)$_3$], 100.2 (1 C, C-3a), 127.5 (1 C, C-6'), 130.0 (1 C, C-5'), 130.7 (1 C, C-4'), 131.8 (1 C, C-2'), 132.1 (1 C, C-3'), 132.9 (1 C, C-1'), 139.0 (1 C, C-3), 153.2 (1 C, C-7a), 154.4 (1 C, C-6) and 157.6 (1 C, C-4).

4-Amino-1-*tert*-butyl-3-(*m*-chlorophenyl)pyrazolo[3,4-*d*]pyrimidine 8e. (0.9 g, 82%), mp 188 °C (Found: M^+, 301.112 80. $C_{15}H_{16}ClN_5$ requires *M*, 301.109 42); δ_H(500 MHz; [$^2H_6$]-DMSO) 1.76 (9 H, s, Bu^t), 6.70 (2 H, br s, NH_2), 7.51 (1 H, dd, ^3J 8.0, ^4J 1.9, 4'-H), 7.54 (1 H, dd, ^3J 7.9, ^3J 7.9, 5'-H), 7.60 (1 H, dd, ^3J 7.3, ^4J 1.6, 6'-H), 7.65 (1 H, dd, ^4J 1.7, ^4J 1.7, 2'-H) and 8.24 (1 H, s, 6-H); δ_C(99.7 MHz; [$^2H_6$]DMSO) 28.7 [3 C, C(*C*H$_3$)$_3$], 59.9 [1 C, *C*(CH$_3$)$_3$], 98.6 (1 C, C-3a), 127.0 (1 C, C-6'), 128.0 (1 C, C-5'), 128.24 (1 C, C-2'), 130.9 (1 C, C-4'), 133.6 (1 C, C-3'), 135.2 (1 C, C-1'), 140.3 (1 C, C-3), 154.0 (1 C, C-7a), 154.7 (1 C, C-6) and 158.2 (1 C, C-4).

4-Amino-3-(*p*-chlorophenyl)-1-cyclohexylpyrazolo[3,4-*d*]pyrimidine 8g. Pyrazole **4g** (500 mg, 1.66 mmol) and formamide (6 ml) gave **8g** (525 mg, 96%), mp 159 °C (Found: C, 62.2; H, 5.6; N, 21.4. $C_{17}H_{18}ClN_5$ requires C, 62.3; H, 5.5; N, 21.4%); δ_H(400 MHz; [$^2H_6$]DMSO) 1.24 (2 H, m, cyclohexyl), 1.44 (2 H, m, cyclohexyl), 1.68 (1 H, m, cyclohexyl), 1.89 (5 H, m, cyclohexyl), 4.66 (1 H, m, NC*H*) 6.90 (2 H, br s, NH_2) 7.55 (2 H, m, 3'-H, 5'-H), 7.66 (2 H, m, 2'-H, 6'-H) and 8.22 (1 H, s, 6-H); δ_C(99.7 MHz; [$^2H_6$]DMSO) 24.9 (1 C, C-4''), 25.0 (2 C, C-3'', C-5''), 31.9 (2 C, C-2'', C-6''), 55.4 (1 C, NCH), 97.3 (1 C, C-3a), 129.0 (2 C, C-3', C-5'), 130.0 (2 C, C-2', C-6'), 131.9 (1 C, C-1'), 133.2 (1 C, C-4'), 142.0 (1 C, C-3), 153.5 (1 C, C-7a), 155.4 (1 C, C-6) and 158.1 (1 C, C-4).

4-Amino-3-(*p*-chlorophenyl)-1-cyclohexyl-6-methylpyrazolo-[3,4-*d*]pyrimidine 9g

Pyrazole **4g** (500 mg, 1.66 mmol), acetonitrile (4 ml) and methanolic ammonia (saturated at room temperature; 15 ml) were stirred at 180–190 °C (internal temperature) in a Teflon-lined autoclave for 42 h. Then the solvents were evaporated and the residue chromatographed (silica gel; light petroleum–*tert*-butyl methyl ether, 1:1) to yield the title compound **9g** (340 mg, 60%), mp 163–165 °C (Found: M^+, 341.13980. $C_{18}H_{20}ClN_5$ requires *M*, 341.14072); δ_H(400 MHz; [$^2H_6$]DMSO) 1.30 (1 H, m, cyclohexyl), 1.52 (2 H, m, cyclohexyl), 1.75 (2 H, m, cyclohexyl), 2.00 (5 H, m, cyclohexyl), 2.58 (3 H, s, 6-Me), 4.76 (1 H, m, NC*H*) 5.42 (2 H, s, NH_2), 7.48 (2 H, m, 3'-H, 5'-H) and 7.63 (2 H, m, 2'-H, 6'-H); δ_C(99.7 MHz; [$^2H_6$]DMSO) 25.2 (1 C, C-4''), 25.5 (2 C, C-3'', C-5''), 26.0 (1 C, Me-6), 32.4 (2 C, C-2'', C-6''), 55.7 (1 C, N*C*H), 96.5 (1 C, C-3a), 129.4 (2 C, C-3', C-5'), 129.8 (2 C, C-2', C-6'), 132.3 (1 C, C-1'), 134.9 (1 C, C-4'), 142.3 (1 C, C-3), 154.9 (1 C, C-7a), 157.2 (1 C, C-4) and 165.2 (1 C, C-6).

4-Amino-1-*tert*-butyl-3-(*p*-methoxyphenyl)-6-phenylpyrazolo-[3,4-*d*]pyrimidine 10b

Pyrazole **4b** (500 mg, 1.85 mmol), benzonitrile (1 ml) and methanolic ammonia (saturated at room temperature; 15 ml) were stirred at 190–200 °C (internal temperature) in a Teflon-lined autoclave for 16 h. Then the solvents were evaporated and the residue chromatographed (silica gel; light petroleum–*tert*-butyl methyl ether, 1:1) to yield the title compound **10b** (136 mg, 20%), mp 166 °C (Found: C, 70.7; H, 6.1; N, 18.6. $C_{22}H_{23}N_5O$ requires C, 70.75; H, 6.2; N, 18.8%); δ_H(250 MHz; [$^2H_6$]DMSO) 1.81 (9 H, s, Bu^t), 3.82 (3 H, s, OC*H*$_3$), 6.80 (2 H, br s, NH_2), 7.10 (2 H, m, 2'-H, 6'-H), 7.48 (3 H, m, 2''-H, 4''-H, 6''-H), 7.60 (2 H, m, 3'-H, 5'-H) and 8.42 (2 H, m, 3''-H, 5''-H); δ_C(124.6 MHz; [$^2H_6$]DMSO) 28.8 [3 C, C(*C*H$_3$)$_3$)], 55.2 (1 C, O*C*H$_3$), 59.5 [1 C, *C*(CH$_3$)$_3$], 97.5 (1 C, C-3a), 114.5 (2 C, C-3', C-5'), 125.6 (1 C, C-1'), 127.8 (2 C, C-3'', C-5''), 128.3 (2 C, C-2'', C-6''), 129.6 (2 C, C-2', C-6'), 130.1 (1 C, C-1''), 138.2 (1 C, C-4''), 141.6 (1 C, C-3), 155.0 (1 C, C-7a), 158.2 (1 C, C-4), 159.5 (1 C, C-4') and 159.6 (1 C, C-6).

4-Amino-1-*tert*-butyl-3,6-diphenylpyrazolo[3,4-*d*]pyrimidine 10a

Sodium (230 mg, 10.0 mmol) was dissolved in dry ethanol (20 ml), and pyrazole **4a** (1.201 g, 5.0 mmol) and benzonitrile (773 mg, 7.5 mmol) were added. After refluxing for 30 h the reaction was quenched with brine and then extracted with ethyl acetate (2 × 40 ml). The organic layer was dried over $MgSO_4$ and the residue purified by chromatography (silica gel; light petroleum–*tert*-butyl methyl ether, 3:1) to yield the title compound **10a** (1.08 g, 63%), mp 164 °C (Found: C, 73.15; H, 6.1; N, 20.3. $C_{21}H_{21}N_5$ requires C, 73.4; H, 6.2; N, 20.4%); δ_H(250 MHz; [$^2H_6$]DMSO) 1.82 (9 H, s, Bu^t), 6.70 (2 H, br s, N*H*$_2$), 7.50 (6 H, m, 2'-H, 4'-H, 6'-H, 2''-H, 4''-H, 6''-H), 7.67 (2 H, m, 3'-H, 5'-H) and 8.41 (2 H, m, 3''-H, 5''-H); δ_C(124.6 MHz; [$^2H_6$]DMSO) 28.9 [3 C, C(*C*H$_3$)$_3$], 59.7 [1 C, *C*(CH$_3$)$_3$], 97.5 (1 C, C-3a), 127.9 (2 C, C-3'', C-5''), 128.2 (2 C, C-2'', C-6''), 128.3 (2 C, C-3', C-5'), 128.4 (1 C, C-4'), 129.0 (2 C, C-2', C-6'), 130.1 (1 C, C-1''), 133.3 (1 C, C-1'), 138.1 (1 C, C-4''), 141.7 (1 C, C-3), 155.1 (1 C, C-7a), 158.2 (1 C, C-4) and 159.6 (1 C, C-6).

1-*tert*-Butyl-3-methyl-5-phenylpyrazole 7a

Method A. Benzoylacetone **5a** (810 mg, 5 mmol) and *tert*-butylhydrazine hydrochloride (630 mg, 5 mmol) were dissolved in dry THF (25 ml), and triethylamine (506 mg, 5 mmol) was added. After refluxing for 8.5 h the solvent was evaporated, the residue redissolved in *tert*-butyl methyl ether and extracted with water (2 × 25 ml). The organic layer was dried over $MgSO_4$ and evaporated to yield the pyrazole **7a** (1.05 g, 98%), mp 98 °C (Found: C, 78.2; H, 8.5; N, 13.1. $C_{14}H_{18}N_2$ requires C, 78.5; H, 8.5; N, 13.1%); δ_H(500 MHz; $CDCl_3$) 1.43 (9 H, s, Bu^t), 2.29 (3 H, s, 3-Me), 5.92 (1 H, s, 4-H) and 7.35 (5 H, m, 5-phenyl).

Method B. Benzoylacetone **5a** (810 mg, 5.0 mmol), *tert*-butylhydrazine hydrochloride (630 mg, 5.0 mmol) and tetrabutylammonium bromide (161 mg, 0.5 mmol) were refluxed in dry THF (25 ml) for 5.5 h. The solvent was evaporated, the residue redissolved in *tert*-butyl methyl ether and was extracted with 5% aqueous sodium hydroxide (25 ml) and water (25 ml). The organic layer was dried over $MgSO_4$ and evaporated to yield pyrazole **7a** (1.08 g, 99%) identical with that described above.

Method C. Benzoylacetone **5a** (810 mg, 5 mmol), *tert*-butylhydrazine hydrochloride (630 mg, 5 mmol) and triethylamine (506 mg, 5 mmol) were refluxed in ethanol (20 ml) for 3 h. Brine (20 ml) was added and the mixture was extracted with *tert*-butyl methyl ether (3 × 30 ml). Drying the organic layer over $MgSO_4$ and evaporation gave **7a** (1.060 g, 99%) identical with that described above.

1-*tert*-Butyl-5-(*p*-chlorophenyl)-3-methylpyrazole 7b

p-Chlorobenzoylacetone **5b** (983 mg, 5 mmol) was treated according to Method C to yield pyrazole **7b** (1.24 g, 99%), mp 158–160 °C (Found: M^+, 248.10904. $C_{14}H_{17}ClN_2$ requires *M*, 248.10803); δ_H(250 MHz; $CDCl_3$) 1.42 (9 H, s, Bu^t), 2.28 (3 H, s, 3-Me), 5.88 (1 H, s, 4-H), 7.25 (2 H, m, 3'-H, 5'-H) and 7.35 (2 H, m, 2'-H, m, 6'-H).

1-Cyclohexyl-3-methyl-5-phenylpyrazole 7c and 1-cyclohexyl-5-methyl-3-phenylpyrazole 6c

Benzoylacetone **5a** (405 mg, 2.5 mmol), triethylamine (253 mg, 2.5 mmol) and cyclohexylhydrazine hydrochloride (377 mg, 2.5

Table 4 Crystallographic data for **4a**, **4b**, **4e**, **4f**, **7c**, **8c** and **8e**[a]

	4a	4b	4e	4f	7c	8c	8e
Empirical formula	$C_{14}H_{16}N_4$	$C_{15}H_{18}N_4O$	$C_{14}H_{15}N_4Cl$	$C_{14}H_{15}N_4Cl$	$C_{16}H_{20}N_2$	$C_{15}H_{16}N_6O_2$	$C_{15}H_{16}N_5Cl$
M	240.3	270.3	274.8	274.8	240.3	312.3	301.8
Colour, habit	clear blocks	clear needles	clear plates	clear needles	clear needles	yellow plates	clear plates
Crystal size/mm	0.50, 0.40, 0.33	0.90, 0.15, 0.13	0.39, 0.24, 0.04	0.59, 0.02, 0.01	0.50, 0.27, 0.23	0.47, 0.47, 0.03	0.26, 0.16, 0.02
Crystal system	monoclinic	triclinic	orthorhombic	triclinic	triclinic	monoclinic	monoclinic
Space group	$P2_1/n$	$P\bar{1}$	$Pmnb$	$P\bar{1}$	$P\bar{1}$	$P2_1/n$	$P2_1/n$
a/Å	10.397(2)	6.224(2)	7.039(2)	6.222(4)	9.734(4)	10.545(2)	12.104(2)
b/Å	9.321(2)	9.556(3)	9.884(2)	9.703(7)	15.247(3)	10.993(2)	10.385(2)
c/Å	14.056(3)	12.806(4)	20.000(4)	12.055(6)	20.179(8)	13.695(2)	12.550(2)
α/°	90	74.52(2)	90	100.21(2)	81.50(2)	90	90
β/°	102.21(2)	84.36(2)	90	93.61(2)	78.02(2)	100.90(2)	97.07(2)
γ/°	90	78.03(2)	90	102.25(2)	83.65(2)	90	90
V/Å^3	1331.5(6)	717.3(4)	1391.5(5)	696.1(8)	2887(2)	1558.9(3)	1565.4(4)
Z	4	2	4[b]	2	8[c]	4	4
D_c/g cm^3	1.199	1.252	1.311	1.311	1.106	1.331	1.280
Radiation	Mo-Kα[d]	Cu-Kα[d]	Cu-Kα[d]	Cu-Kα[e]	Cu-Kα[e]	Cu-Kα[d]	Cu-Kα[e]
μ/mm^{-1}	0.075	0.657	2.357	2.356	0.498	0.771	2.163
F(000)	512	288	576	288	1040	656	632
2θ Range/°	7–45	3–120	3–125	1–116	3–120	3–120	3–116
Independent reflections (R_{Int})	2344 (0.01)	2124 (0.00)	1205 (0.00)	1936 (0.00)	8557 (0.00)	2310 (0.02)	2182 (0.05)
Observed reflections [$F_o > 4\sigma(\|F_o\|)$]	1587	1877	878	1300	6190	1819	1385
Max./min. transmission	N/A	N/A	0.918/0.621[f]	N/A	N/A	N/A	N/A
Number of parameters	172	190	146	181	650	217	199
g in weighting scheme[g]	0.0007	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005
Final $R(R_w)$	0.046 (0.051)	0.045 (0.054)	0.055 (0.064)	0.057 (0.058)	0.050 (0.054)	0.054 (0.055)	0.075 (0.078)
Largest and mean Δ/σ	0.055, 0.002	0.093, 0.005	0.068, 0.009	0.018, 0.003	0.001, 0.000	0.019, 0.001	0.004, 0.000
Data/parameter ratio	9.23	9.88	6.01	7.18	9.52	8.38	6.96
Largest difference peak, hole/e Å^{-3}	0.18, −0.15	0.19, −0.16	0.23, −0.23	0.34, −0.26	0.16, −0.19	0.31, −0.24	0.26, −0.46

[a] Details in common: Graphite monochromated radiation, ω-scans, room temperature, refinement based on F. [b] The molecule has crystallographic C_s symmetry. [c] There are four crystallographically independent molecules in the asymmetric unit. [d] Siemens P4/PC diffractometer. [e] Siemens P4/RA diffractometer. [f] Face-indexed numerical absorption correction applied. [g] $w^{-1} = \sigma^2(F_o) + g(F_o^2)$.

mmol) in ethanol (10 ml) was treated according to method C. The regioisomers were separated by chromatography (silica gel; light petroleum–ethyl acetate, 95:5) to yield pyrazole **6c** (77 mg, 13%) as an oil and pyrazole **7c** (480 mg, 80%) as colourless crystals, mp 44 °C; **6c** (Found: M$^+$, 240.16346. $C_{16}H_{20}N_2$ requires M, 240.16265); δ_H(250 MHz; $CDCl_3$) 1.30 (3 H, m, cyclohexyl), 1.65 (1 H, m, cyclohexyl), 1.85 (4 H, m, cyclohexyl), 2.05 (2 H, m, cyclohexyl), 2.30 (3 H, d, ^4J 0.6, 5-Me), 3.96 (1 H, tt, ^3J 11.0, ^3J 4.2, NCH), 6.27 (1 H, d, ^4J 0.6, 4-H), 7.20 (1 H, m, 4′-H), 7.35 (3′-H, 5′-H) and 7.75 (2 H, m, 2′-H, 6′-H). **7c** (Found: M$^+$, 240.16329. $C_{16}H_{20}N_2$ requires M, 240.16265); δ_H(250 MHz; $CDCl_3$) 1.30 (3 H, m, cyclohexyl), 1.60 (1 H, m, cyclohexyl), 1.85 (4 H, m, cyclohexyl), 2.05 (2 H, m, cyclohexyl), 2.32 (3 H, s, 3-Me), 4.02 (1 H, tt, ^3J 11.5, ^3J 4.0, NC*H*), 6.01 (1 H, s, 4-H), 7.35 (3′-H, 5′-H) and 7.41 (3 H, m, 2′-H, 4′-H, 6′-H).

Crystal data

Table 4 provides a summary of the crystal data, data collection, and refinement parameters for compounds **4a**, **b**, **e**, **f**, **7c**, **8c** and **8e**, data in each case having been corrected for Lorentz and polarisation factors, and for absorption as indicated. All the structures were solved by direct methods and their non-hydrogen atoms were refined anisotropically,[18] with the exception of **4e** where there is 80:20 disorder in the position of the *meta*-chlorophenyl substituent and the minor occupancy carbon atoms were refined isotropically. The positions of the amino hydrogen atoms in all the structures were determined from ΔF maps and were refined isotropically subject to an N–H distance constraint. The positions of the remaining hydrogen atoms were idealised, assigned isotropic thermal parameters [U(H) = 1.2U_{eq}(C)] and allowed to ride on their parent carbon atoms. Atomic coordinates, thermal parameters and bond length and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/20.

Acknowledgements

We are grateful to ICON (Mr P. Docx) and SPECS and BioSPECS (Dr R. L. Wife) for financial support for U. H. and to the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College.

References

1 R. M. Acheson, *An Introduction to the Chemistry of Heterocyclic Compounds*, Wiley, New York, London, Sydney, 2nd ed., 1967, p. 309.
2 L. Claisen and E. Haase, *Chem. Ber.*, 1895, **28**, 35.
3 A. Michaelis and E. Remy, *Chem. Ber.*, 1907, **40**, 1020.
4 P. Schmidt, K. Eichenberger, M. Wilhelm and J. Druey, *Helv. Chim. Acta*, 1959, **42**, 763.
5 S. M. Hecht and D. Werner, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1903.
6 C. B. Ziegler, Jr., N. A. Kuck, S. M. Harris and Yang-i Lin, *J. Heterocycl. Chem.*, 1988, **25**, 1543.
7 C. C. Cheng and R. K. Robins, *J. Org. Chem.*, 1956, **21**, 1240.
8 P. L. Southwick and B. Dhawan, *J. Heterocycl. Chem.*, 1975, **12**, 1199.
9 N. I. Ghali, D. L. Venton, S. C. Hung and G. C. Le Breton, *J. Org. Chem.*, 1981, **46**, 5413.
10 R. K. Robins, *J. Am. Chem. Soc.*, 1956, **78**, 784.
11 G. Levesque, J-C. Gressier and M. Proust, *Synthesis*, 1981, 963.
12 R. R. Roberts, S. R. Landor and E. A. Bolessa, *Tetrahedron Lett.*, 1994, **35**, 3021.
13 H. Wamhoff and L. Lichtenthäler, *Chem. Ber.*, 1978, **111**, 2297.

14 T. Huynh Dinh, A. Kolb, G. Barnathan and J. Igolen, *J. Chem. Soc., Chem. Commun.*, 1973, 680; H. Bader, J. D. Downer and P. Driver, *J. Chem. Soc.*, 1950, 2775.
15 F. Seela and H. Winter, *Helv. Chim. Acta*, 1994, **77**, 597.
16 E. C. Taylor and A. L. Borror, *J. Org. Chem.*, 1961, **26**, 4967.
17 A. Dornow and H. Grabhöfer, *Chem. Ber.*, 1958, **91**, 1824.
18 SHELXTL PC ver. 4.2, Siemens Analytical X-Ray Instruments, Madison, WI, 1990

Paper 5/08246C
Received 19*th December* 1995
Accepted 8*th March* 1996