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Synthesis and chemistry of 3-*tert*-butyl-1,5-diaminopyrazole †

Alexander J. Blake,[a] David Clarke,[b] Richard W. Mares[c] and Hamish McNab*[c]

[a] *School of Chemistry, The University of Nottingham, University Park, Nottingham, UK NG7 2RD*

[b] *Kodak European Research and Development, Headstone Drive, Harrow, Middlesex, UK HA1 4TY*

[c] *School of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh, UK EH9 3JJ*

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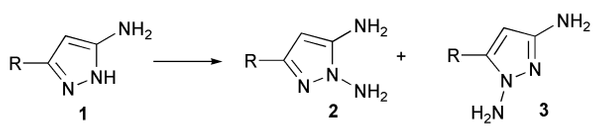
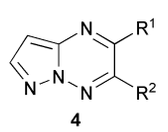
N-Amination of 3-amino-5-*tert*-butylpyrazole **11** with hydroxylamine-*O*-sulfonic acid gave the 1,5-diaminopyrazole **12** with good regiochemical control. The reactions of **12** with certain electrophiles (*e.g.* acetic anhydride, DMF acetal, aromatic aldehydes, methoxymethylene Meldrum's acid) took place at one (or both) of the amino groups and no cyclised products were obtained. Reaction of **12** with carbon disulfide followed by alkylation under basic conditions provided the pyrazolo[1,5-*b*]1,2,4-triazole **26** which is a useful photographic magenta coupler. Reactions of **12** with 1,2- and 1,3-dicarbonyl compounds (diketones and ketoesters) provided new pyrazolo[1,5-*b*]1,2,4-triazines **29**, **30**, **42** and **43** and the first derivatives of the pyrazolo[1,5-*b*]1,2,4-triazepine system **31** and **35**–**36**. The X-ray crystal structure of the pyrazolotriazepine **33** is reported.

Although vicinal diamines are important intermediates in the synthesis of heterocycles, very little work has been published on the 1,5-diaminopyrazole system **2**. The problem is that *N*-amination of most 3-aminopyrazoles **1** proceeds with little regioselectivity under standard conditions and mixtures of 1,5-diamino- and 1,3-diamino- pyrazole isomers **2** and **3** respectively are obtained which are separable only with difficulty (Scheme 1).[1,2] The aim of the present work was to find conditions of reagent or substrate which might improve the regioselectivity of this amination reaction so that the properties – in particular heterocyclisation reactions – of the 1,5-diaminopyrazole unit **2** could be explored in detail. Only one type of heterocyclisation reaction is known in this series; Sliskovic *et al.* reported condensation of **2** (R = H) with 1,2-dialdehydes, 1,2-diketones and 2-ketoaldehydes to give derivatives of the pyrazolo[1,5-*b*]1,2,4-triazine ring system **4**.[1,3]



Scheme 1

As found by the previous workers,[1] reaction of 3-aminopyrazole **5** with hydroxylamine-*O*-sulfonic acid gave a 1 : 1 mixture of amination products **6** and **7**. The ^{1}H NMR chemical shifts of 4-position resonances of the amination products appeared at lower frequencies (by 0.2–0.3 ppm) than that of the starting material **5**. Attempted *in situ* cyclisation reactions of **6** were unsuccessful. The regioselectivity was only marginally improved by amination of 3-amino-5-methylpyrazole **8**; in this case **9** and **10** were obtained in a 60 : 40 ratio. However, reaction of 3-amino-5-*tert*-butylpyrazole **11** with hydroxylamine-*O*-sulfonic acid under the standard conditions showed much greater selectivity. Although three signals were present in the region of the 4-proton resonances in the ^{1}H NMR spectrum of the product mixture, the required 1,5-aminopyrazole **12** (δ_H 5.21) was the major product (57%) together with unreacted starting material **11** (δ_H 5.40) (40%) and only a small peak at δ_H 5.30 (*ca.* 3%) which was assigned to the 1,3-diamino isomer **13**. The *tert*-butyl group clearly had the desired effect in controlling the regiochemistry of the *N*-amination process. In one other example of a 5-substituent directing the nucleophilic reactivity towards the 2-heteroatom in 3-aminopyrazole systems, a bulky *tert*-butyl group is apparently unnecessary.[4]



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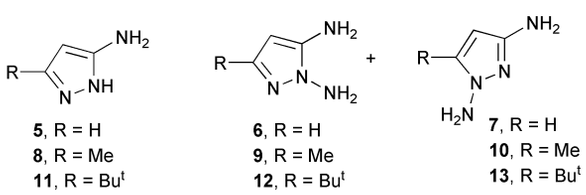


5, R = H
8, R = Me
11, R = Bu^t

6, R = H
9, R = Me
12, R = Bu^t

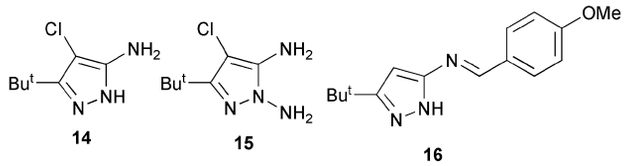
7, R = H
10, R = Me
13, R = Bu^t

Next, it was important to develop conditions which would allow the *N*-amination process to be driven to completion, since separation of **11**–**13** by Kugelrohr distillation was ineffective and chromatography proved time-consuming and low-yielding. Use of two equivalents of aminating agent gave an increased amount of products but starting material was still present; the situation was not improved by use of three or four equivalents of reagent which led to the presence of impurities in the final product. The optimum method, reported in detail in the Experimental section, involved treatment of **11** with a two-fold excess of hydroxylamine-*O*-sulfonic acid in DMF, followed by work-up and repeat reaction with a further two equivalents of aminating agent. Yields of 60–70% of **12** and its 4-chloro derivative **15** could be routinely achieved. However, attempted amination of the imine **16** was unsuccessful and only the amine **11** and anisaldehyde were recovered.

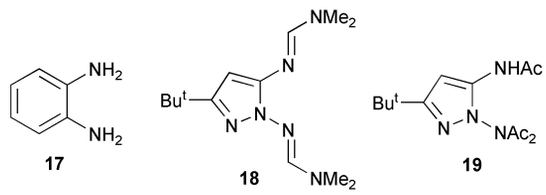
The reactivities of the amino groups of **12** were then probed by reaction of the diamine with a range of mono-functionalised electrophiles, by analogy with the chemistry of *o*-phenylenediamine **17**. Thus treatment of **12** with an excess of DMF acetal

† CCDC reference number 211651. See http://www.rsc.org/suppdata/ob/b3/b306058f/ for crystallographic data in .cif or other electronic format.

DOI: 10.1039/b306058f



gave a product in almost quantitative yield which showed the molecular mass expected of the bis-amidine **18**. In agreement with this, the product showed two methine singlets (δ_H 8.27 and 7.74) and broad signals in the *N*-methyl region of the ^{13}C NMR spectrum (δ_C 34.1–40.1) consistent with restricted rotation around the N–C bonds. No clearly defined products could be obtained by reaction of **12** with triethyl orthoformate. Under comparable conditions, reaction of *o*-phenylenediamine either with DMF acetal[5] or with trimethyl orthoformate[6] gives benzimidazole. These results establish that the reactivity of **12** is fundamentally different to that of a simple aromatic diamine, probably because of the additional strain in fused 5–5 ring systems compared with that in fused 6–5 systems.

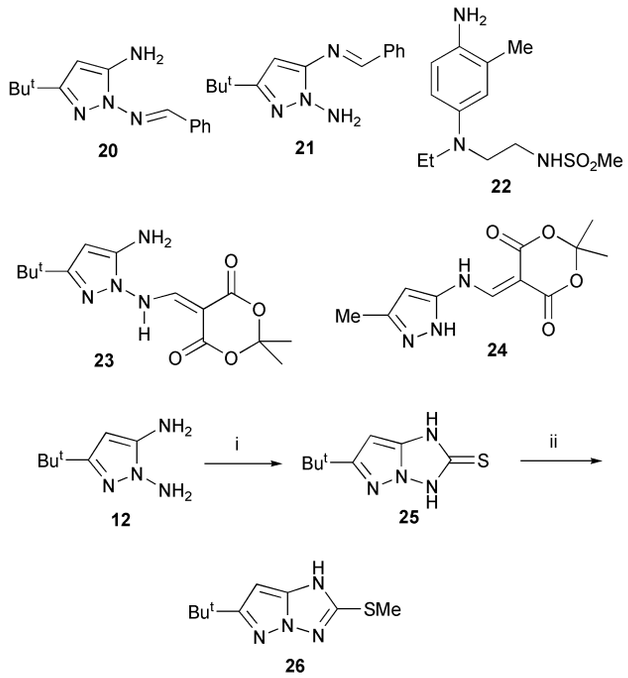


Reaction of **12** with an excess of acetic anhydride gave a triacetyl derivative (25%), thought to be **19** by analogy with results quoted below. Other acylated products were present but were not characterised, though it was clear that no cyclisation reactions had occurred.

Other electrophiles were more selective and reacted only at one of the amino groups of **12**. Thus benzaldehyde gave a single monoimine (72%) (which could either be **20** or **21**), characterised by the imine resonance at δ_H 8.88 and a pyrazole ring signal at δ_H 5.41. The pyrazole ring resonance of the *N*-unsubstituted imine **16** (δ_H 6.10) is significantly deshielded relative to this value, which suggests that the structure of the product is **20**, *i.e.* the *N*-amino function is the more reactive of the two amines. This conclusion was confirmed by spraying a TLC spot of the imine product (**20/21**), with the developer **22** in the presence of an oxidising agent (potassium persulfate).[7] This produced a coloured spot (cyan), which would be expected only if the 5-amino group was available for electron donation into the pyrazole ring.

Similarly, reaction of **12** with methoxymethylene Meldrum's acid in acetonitrile solution gave a single mono-'Meldrumsated' product (37%) which was assigned the structure **23** by analogy with the work described in the previous paragraph. In addition, the pyrazole methine signal (at δ_C 87.11) is significantly shielded relative to the signal due to the corresponding position of **24**[8] (δ_C 93.49) which provides further evidence for 'Meldrumsation' at the 1-position of **12**. The presence of a methine signal at δ_C 152.21 in the ^{13}C NMR spectrum of **23** confirms that an unsaturated 5-methylene moiety is still present in the product and hence that cyclisation of the remaining NH_2 group at the methylene position has not taken place.

In contrast to the above results, a cyclised product was successfully obtained when **12** was reacted with carbon disulfide in the presence of base (Scheme 2). There is some precedent for this reaction, even in the 5–5 fused ring series.[9] On work-up of the thione **25** a semi-solid was obtained which showed many spots by TLC, but the mixture was directly alkylated (iodomethane, base) and the pyrazolo[1,5-*b*]1,2,4-triazole **26** was isolated as a yellow solid after column chromatography in 5.5% (unoptimised) yield. The product was characterised by mass spectrometry (*m*/*z* 210, M^+, 81%) and by ^1H NMR

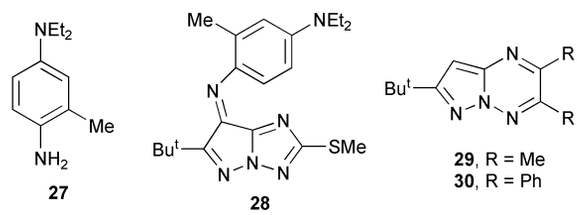


Scheme 2 *Reagents and conditions:* i, CS_2, base, ii, MeI, base.

spectroscopy which showed a signal at δ_H 5.61 due to the ring proton at the electron rich 7-position.

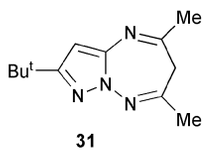
These reactions of the diamine **12** therefore provide a novel route to the pyrazolo[1,5-*b*]1,2,4-triazole system, which is an important magenta coupler in colour photography.[10] The 2-methylthio compound **26** is a new derivative of this system and its properties as a coupler were therefore investigated.[11] Treatment of **26** with the developer **27** in the presence of potassium persulfate provided the azomethine dye **28** (81% isolated yield) [λ_{max} (EtOAc) 546 nm, ε 5.8 × 10^{-4}, $w_{½}$ 66 nm], which shows none of the secondary blue absorptions found in certain other magenta coupler series. The absorption maximum is strongly solvent dependent; changing the solvent from cyclohexane to methanol causes a bathochromic shift of 34 nm. The 2-methylthio group causes a bathochromic shift of 16 nm in the absorption maximum by comparison with the effect of a methyl group at the same position.[12]

The diamine **12** was also reacted with a range of 1,2- and 1,3-dicarbonyl compounds which provided a good route to fused 5–6 and 5–7 heterocyclic systems with a consecutive array of three nitrogen atoms. As found by Sliskovic and co-workers for the parent 1,5-diaminopyrazole,[1] reaction of **12** with butanedione or with benzil in acetic acid gave the pyrazolo-[1,5-*b*]1,2,4-triazines **29** (54%) and **30** (27%) respectively.



Reaction of **12** with acetylacetone in refluxing acetic acid provided the first example of the pyrazolo[1,5-*b*]1,2,4-triazepine system **31**. The product was obtained as an oil (39% yield) after chromatography on alumina. Compound **31** adopts the 3*H* tautomer exclusively, even in hydrogen bond acceptor solvents such as [$^2H_6$]acetone. By analogy with the 1,5-benzodiazepine system, which adopts an analogous tautomer, the seven membered ring of **31** is likely to be non-planar and interconversion between two equivalent forms may be reflected in the coalescence behaviour of the methylene protons. For

example, these signals of the 1,5-benzodiazepine **32** show a coalescence temperature of −50 °C corresponding to an activation energy barrier to ring inversion of 49.8 kJ mol^{-1}.[13] However, the methylene protons of the pyrazolo[1,5-*b*]1,2,4-triazepine **31** (H-3) occur as a singlet in the ^{1}H NMR spectrum ([$^2H_6$]acetone solvent) at δ_H 3.18 at temperatures as low as −100 °C, indicating that the fused 5–7 pyrazolo[1,5-*b*]1,2,4-triazepine system is much more flexible than the fused 6–7 1,5-benzodiazepine (see also below).



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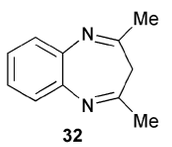

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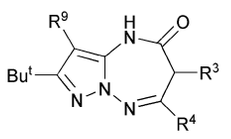


33 $R^3 = R^9 = H$, $R^4 = Me$
34 $R^3 = R^4 = Me$, $R^9 = H$
35 $R^3 = R^9 = H$, $R^4 = Pr^n$
36 $R^3 = H$, $R^4 = Me$, $R^9 = Cl$

β-Ketoesters also react with the diaminopyrazoles **12** and **15** in refluxing acetic acid (1–1.5 h) to give pyrazolo[1,5-*b*]1,2,4-triazepin-2-ones **33**–**36**. Compounds **33**–**35** were prepared in 42–55% yield using the appropriate ketoesters, though ethyl benzoylacetate and ethyl pivaloylacetate failed to react, presumably for electronic and steric reasons respectively. When the chloropyrazole **15** was employed, the yield of **36** was almost doubled relative to its unsubstituted analogues (see also below), though the reason for this effect is not clear. The products were characterised by their spectra (see Experimental section) and the regiochemistry of the reaction and tautomeric form of the products were established by an X-ray crystal structure of the 4-methyl derivative **33** (Fig. 1). The observed regiochemistry suggests that the cyclisation mode is determined by reaction of the more reactive *N*-amino function of the diaminopyrazole with the ketonic carbonyl group of the ketoester. A similar tautomeric form to **33** is adopted by the related 1,5-benzodiazepine derivative **37**, though the dihydrodiazepine **38** is instead an enamine in solution and in the solid state.[14] The crystal structure of **33** additionally shows the planarity of the 5-membered ring (to within 0.007 Å) and the boat-shape adopted by the 7-membered ring (Fig. 1).

The geometric parameters of **33** are generally unexceptional. For example, those of the 5-membered ring are close to those of

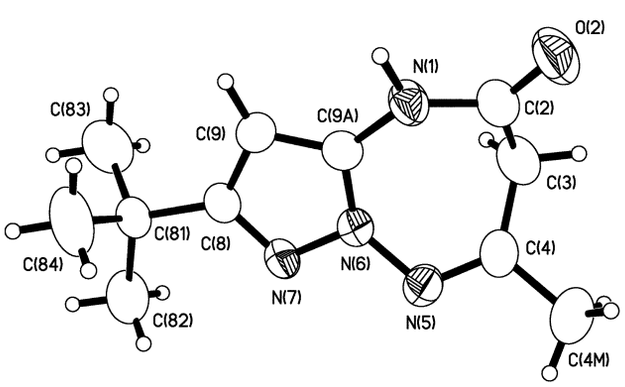
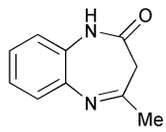


Fig. 1 A view of the crystal structure of the pyrazolotriazepinone **33**. Displacement ellipsoids are drawn at the 50% probability level. Selected bond lengths/Å: N(1)–C(2) 1.360(5), N(1)–C(9a) 1.386(5), C(2)–O(2) 1.210(5), C(2)–C(3) 1.500(6), C(3)–C(4) 1.490(6), C(4)–N(5) 1.283(5), N(5)–N(6) 1.389(4), N(6)–C(9a) 1.358(5), N(6)–N(7) 1.363(4), N(7)–C(8) 1.331(4), C(8)–C(9) 1.402(5), C(9)–C(9a) 1.354(5); selected bond angles/°: C(2)–N(1)–C(9a) 127.1(3), N(1)–C(2)–C(3) 115.2(4), C(4)–C(3)–C(2) 114.3(4), N(5)–C(4)–C(3) 124.8(4), C(4)–N(5)–N(6) 116.5(3), C(9a)–N(6)–N(7) 111.6(3), C(9a)–N(6)–N(5) 131.9(3), N(7)–N(6)–N(5) 114.3(3), C(8)–N(7)–N(6) 104.8(3), N(7)–C(8)–C(9) 110.8(3), C(9a)–C(9)–C(8) 106.1(3), C(9)–C(9a)–N(6) 106.7(3), N(1)–C(9a)–C(9) 128.8(3), N(6)–C(9a)–N(1) 124.3(3).



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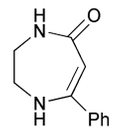

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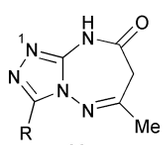
1-aminopyrazole;[15] even the N(5)–N(6) distance [1.389(4) Å] is coincidentally close to the corresponding exocyclic N–N bond length in 1-aminopyrazole [1.403(2) Å]. Except for the bond angles at the pyrazole ring, which are close to typical values, the other angles at the ring junctions of **33** are distorted. In particular the endocyclic angle C(9a)–N(6)–N(5) [131.9(3)°] and the exocyclic angle N(1)–C(9a)–C(9) [128.8(3)°] are much larger than expected. Intermolecular contacts include an N–H ··· O hydrogen bond linking a-glide related molecules into chains running along the [100] direction. As with the dimethyl derivative **31**, the 3-methylene group of **33** appears as a singlet (δ_H 3.36) in the ^{1}H NMR spectrum at temperatures as low as −80 °C, so that ring inversion is fast on the NMR time scale. The corresponding benzodiazepin-2-one **37** shows coalescence at −60 °C ($\Delta G^{\#}$ 39.8 kJ mol^{-1}).[12] It appears, therefore, that pyrazolo[1,5-*b*]1,2,4-triazepines are consistently much more flexible than the corresponding benzodiazepines.

Elguero and co-workers have reported that analogous triazolo[4,3-*b*]1,2,4-triazepin-2-ones **39** can undergo an unusual ring contraction on heating in acetic anhydride to give 1-acylated pyrazolo[5,1-*c*]1,2,4-triazoles **40**, by formal loss of HCNO.[16] The reaction is thought to involve initial *N*-acylation at the 1-position.[17] However, reaction of **33** with acetic anhydride under these conditions gave no useful products, possibly owing to the *tert*-butyl group hindering the acylation at position 7 which would be required as the first step of the mechanism.



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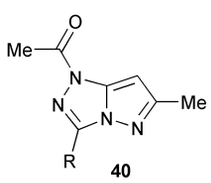

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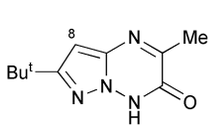
Reaction of **12** with diethyl malonate under comparable conditions gave no cyclised products.

Finally, treatment of **12** with methyl (or ethyl) pyruvate in refluxing acetic acid for 1.5 h gave a single solid product whose mass spectrum was consistent with the formation of one of the regioisomers **41** or **42** (32%). Poorer yields were obtained when either longer or shorter reaction times were used, but again the yield was doubled when the chloropyrazole **15** was used as the starting material. The cyclised products proved to be weakly active towards the oxidised coupler **22** which suggests that their structures must be the pyrazolo[1,5-*b*]1,2,4-triazin-2-one (**42** and **43**) since the alternative isomer (*e.g.* **41**) is not activated towards coupling at the 8-position. As found for the β-ketoester condensations described above, the regiochemistry is therefore controlled by reaction of the *N*-amino function with the ketonic carbonyl group.



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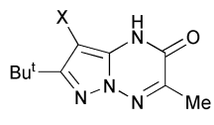

42 X = H
43 X = Cl

In conclusion, we have shown that the simple strategy of increasing the steric bulk at the 5-position of a 3-aminopyrazole dramatically increases the regioselectivity of *N*-amination reactions so that appropriate 1,5-diaminopyrazole

derivatives are now readily available. We have shown that the reactivities of the two amino functions are substantially different, with the *N*-amino group being the more reactive. Balancing the disparate reactivities of these two groups can cause problems with cyclisation reactions particularly when the product consists of two fused 5-membered rings. Nevertheless, a new pyrazolo[1,5-*b*]1,2,4-triazole has been synthesised and its application as a photographic magenta coupler examined. Cyclisation reactions with 1,2- and 1,3-dicarbonyl compounds (diketones and ketoesters) were successful giving access to new pyrazolo[1,5-*b*]1,2,4-triazines and pyrazolo[1,5-*b*]1,2,4-triazepines.

Experimental

^{1}H And ^{13}C NMR spectra were recorded at 250 (or 200) and 63 (or 50) MHz respectively for solutions in [^{2}H]chloroform unless otherwise stated. Coupling constants are quoted in Hz. ^{13}C NMR signals refer to CH resonances unless otherwise stated; in most cases assignments were confirmed by appropriate DEPT experiments. Mass spectra were obtained under electron impact conditions.

3-Amino-5-*tert*-butylpyrazole 11 [18]

This product was made by the standard method [18] from hydrazine hydrate (15 g, 15 cm^3, 0.28 mol) and 4,4-dimethyl-3-oxopentanenitrile (18.5 g, 0.15 mol) heated under reflux in ethanol (200 cm^3) for 1 h. After work-up, the crude compound was recrystallised as reported.[18] The yield of the pyrazole was 16.80 g (74%), mp 78–79 °C (lit.,[18] 80 °C). δ_H 5.31 (1H, s), 3.89 (2H, br, s) and 1.19 (9H, s); δ_C 155.18 (quat), 153.62 (quat), 88.93, 30.86 (quat) and 29.88 (CH_3).

3-Amino-5-*tert*-butyl-4-chloropyrazole 14 [19]

3-Amino-5-*tert*-butylpyrazole **11** (1.39 g, 10 mmol) was dissolved in dichloromethane (30 cm^3) and cooled to 0 °C. *N*-Chlorosuccinimide (1.34 g, 10 mmol) was added slowly in small portions and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with saturated sodium bicarbonate solution (3 × 50 cm^3). The organic phase was separated and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* to give a dark coloured solid, which was recrystallised from cyclohexane to give 3-amino-5-*tert*-butyl-4-chloropyrazole **14** as orange–red crystals, 1.25 g (72%), mp 122–123 °C (from cyclohexane). δ_H 6.10 (2H, br, s) and 1.31 (9H, s); δ_C 151.11 (quat), 147.54 (quat), 93.13 (quat), 31.72 (quat) and 27.80 (CH_3); *m*/*z* 175 (M$^+$, 13%), 173 (M$^+$, 40%), 160 (33), 158 (100), 130 (15) and 123 (10). This compound has been previously reported in a Japanese patent.[19]

N-Amination of 3-aminopyrazoles: general method

The aminopyrazole (10 mmol) was dissolved in dry dimethylformamide (15 cm^3) and cooled to −10 °C. Crushed potassium hydroxide (4.16 g) was added and the solution was left to stir for 20 min at −10 °C. Hydroxylamine-*O*-sulfonic acid (2.26 g, 20 mmol) was added cautiously in small portions. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was then filtered and the solvent was removed under reduced pressure. The resulting semi-solid was re-dissolved in dichloromethane, filtered, and dried over anhydrous magnesium sulfate. On removal of the solvent at reduced pressure an oily product was obtained which was found to be a mixture of diamines and starting materials. The mixture was re-dissolved in dimethylformamide and the whole reaction sequence was repeated. The resulting products were distilled under vacuum (Kugelrohr); they could be further purified by dry flash chromatography (50 : 50 ethyl acetate–hexane), but were generally used after distillation. Two diamines were synthesised by this method:

1,5-Diamino-3-*tert*-butylpyrazole 12. (0.92–1.07 g, 60–70%), bp 128–129 °C (0.1 Torr). (Found: M$^+$ 154.1214. $C_7H_{14}N_4$ requires *M* 154.1218); δ_H 5.20 (1H, s), 4.50 (4H, br, s) and 1.19 (9H, s); δ_C 158.10 (quat), 144.43 (quat), 83.35, 31.87 (quat) and 31.10 (CH_3); *m*/*z* 154 (M$^+$, 44%), 139 (81), 124 (100), 122 (16), 112 (22), 109 (97), 95 (12) and 94 (18).

1,5-Diamino-3-*tert*-butyl-4-chloropyrazole 15. (1.15 g, 61%), bp 156–158 °C/0.1 Torr. (Found: M$^+$ 188.0830. $C_7H_{13}{}^{35}ClN_4$ requires *M* 188.0829); δ_H 5.08 (2H, br, s), 4.08 (2H, br, s) and 1.26 (9H, s); δ_C 151.52 (quat), 141.84 (quat), 86.62 (quat), 32.62 (quat) and 28.37 (CH_3); *m*/*z* 190 (M$^+$, 8%), 188 (M$^+$, 26%), 175 (24), 173 (79), 160 (33), 158 (100), 139 (31) and 124 (43).

As reported by Sliskovic,[1] 3-aminopyrazole **5** gave a 1 : 1 mixture of 1,5-diaminopyrazole **6** and 1,3-diaminopyrazole **7** upon amination under standard conditions. Efforts to separate the mixture were unsuccessful.

Amination of 3-amino-5-methylpyrazole **8** gave a 60 : 40 mixture of 1,5-diamino-3-methylpyrazole **9** and 1,3-diamino-5-methylpyrazole **10**. This mixture was also inseparable by standard methods.

1-Aza-1-(5-*tert*-butylpyrazol-3-yl)-2-(4-methoxyphenyl)ethene 16

3-Amino-5-*tert*-butylpyrazole **11** (1.39 g, 10 mmol) was dissolved in absolute ethanol (150 cm^3) and treated with piperidine (1 cm^3) and *p*-anisaldehyde (1.36 g, 1.21 cm^3, 10 mmol). The mixture was heated to reflux for 3 h. On removal of solvent a gummy product was obtained. This was redissolved in ether and removal of solvent gave a solid product identified as *1-aza-1-(5-tert-butylpyrazol-3-yl)-2-(4-methoxyphenyl)ethene* **16** (1.67 g, 65%), mp 138–139 °C (from cyclohexane). (Found: C, 67.85; H, 7.1; N, 15.9. $C_{15}H_{19}N_3O$. 0.5 H_2O requires C, 67.65; H, 7.1; N, 15.8%); δ_H 8.67 (1H, s), 7.80 (2H, d, ^3J 8.7), 6.89 (2H, d, ^3J 8.7), 6.10 (1H, s), 3.78 (3H, s) and 1.32 (9H, s); δ_C 161.88 (quat), 159.14, 157.31 (quat), 156.08 (quat), 130.24, 128.84 (quat), 113.79, 91.20, 55.04 (CH_3), 31.16 (quat) and 29.91 (CH_3); *m*/*z* 257 (M$^+$, 100%), 256 (31), 241 (62), 215 (36), 200 (12) and 134 (52).

Reaction of 1-aza-1-(5-*tert*-butylpyrazol-3-yl)-2-(4-methoxyphenyl)ethene 16 with hydroxylamine-*O*-sulfonic acid

1-Aza-1-(5-*tert*-butylpyrazol-3-yl)-2-(4-methoxyphenyl)ethene **16** (0.257 g, 1 mmol) was dissolved in DMF (2 cm^3). Potassium hydroxide (0.416 g, 7.4 mmol) and hydroxylamine-*O*-sulfonic acid (0.226 g, 2 mmol) were added using the same conditions mentioned previously. The mixture was left stirring for 2 h and DMF was removed *in vacuo*. After further work up with dichloromethane products were isolated which were found to be 5-*tert*-butyl-3-aminopyrazole **11** and anisaldehyde, *i.e.* hydrolysis of the imine had occurred.

1,5-Bis(3,3-dimethyl-1,3-diazapropenyl)-3-*tert*-butylpyrazole 18

1,5-Diamino-3-*tert*-butylpyrazole **12** (0.154 g, 1 mmol) was heated on a steam bath with dimethylformamide dimethylacetal (2 cm^3) for 1 h. On removal of solvent under reduced pressure a white solid was obtained which was identified as the bis-amidine, *1,5-bis-(3,3-dimethyl-1,3-diazapropenyl)-3-tert-butylpyrazole* **18** (0.254 g, 96%), which could not be purified, mp *ca.* 92 °C; (Found: M$^+$ 264.2068. $C_{13}H_{24}N_6$ requires *M* 264.2062); δ_H 8.27 (1H, s), 7.74 (1H, s), 5.52 (1H, s), 2.94–2.90 (12H, m) and 1.21 (9H, s); δ_C 155.88 (quat), 154.54, 154.10, 144.87 (quat), 84.42, 40.11 (CH_3), 37.96 (2CH_3), 34.19 (CH_3), 32.05 (quat) and 30.39 (CH_3); *m*/*z* 264 (M$^+$, 100%), 249 (10), 194 (21), 193 (12), 179 (26), 152 (14) and 138 (24).

Reaction of 1,5-diamino-3-*tert*-butylpyrazole with triethyl orthoformate

1,5-Diamino-3-*tert*-butylpyrazole **12** (0.154 g, 1 mmol) was heated in a Kugelrohr oven to 80 °C with triethyl orthoformate (0.25 cm^3). The by-product ethanol was distilled off, collected and identified by its ^1H NMR spectrum. The mixture was heated until ethanol ceased to evolve. A glassy solid was obtained which appeared to be polymeric.

5-Acetamido-1-(*N,N*-diacetylamino)-3-*tert*-butylpyrazole 19

1,5-Diamino-3-*tert*-butylpyrazole **12** (0.308 g, 2 mmol) was heated under reflux in acetic anhydride (10 cm^3) for 2 h. On cooling a white precipitate was recovered and this was identified as *5-acetamido-1-(N,N-diacetylamino)-3-tert-butylpyrazole* **19** (0.140 g, 25%), mp 220–221 °C (from ethanol). (Found: M^+ 280.1540. $C_{13}H_{20}N_4O_3$ requires *M* 280.1535); δ_H (^{2}[H]$_6$DMSO) 6.43 (1H, s), 2.18 (6H, s), 2.06 (3H, s) and 1.21 (9H, s); δ_C (^{2}[H]$_6$DMSO) 170.47 (quat), 167.33 (quat), 159.81 (quat), 137.85 (quat), 92.00, 32.21 (quat), 30.01 (CH_3), 24.56 (CH_3) and 23.29 (CH_3); *m/z* 280 (M^+, 20%), 238 (93), 196 (100), 154 (33) and 125 (40). Removal of solvent *in vacuo* yielded a yellow oil which was found to be a mixture of triacetylated and diacetylated products.

1-Aza-1-(5-amino-3-*tert*-butylpyrazol-1-yl)-2-phenylethene 20

1,5-Diamino-3-*tert*-butylpyrazole (0.167 g, 1.08 mmol) was condensed with benzaldehyde (0.115 g, 0.110 cm^3) in the presence of toluene-*p*-sulfonic acid (cat.) in methanol (3 cm^3). The mixture was maintained at reflux temperature for 3 h. Removal of solvent gave a brown solid, *1-aza-1-(5-amino-3-tert-butylpyrazol-1-yl)-2-phenylethene* **20** (0.188 g, 72%), mp *ca*. 136 °C. (Found M^+ 242.1527. $C_{14}H_{18}N_4$ requires *M* 242.1531); δ_H 8.88 (1H, s), 7.79 (2H, m), 7.39 (3H, m), 5.41 (1H, s), 4.24 (2H, br, s) and 1.31 (9H, s); δ_C 160.55 (quat), 144.82, 144.04 (quat), 133.9 (quat), 129.59, 128.53, 127.55, 84.85, 32.44 (quat) and 29.99 (CH_3); *m/z* 242 (M^+, 20%), 227 (7), 210 (7), 138 (4) and 124(9).

5-(3-*tert*-Butyl-5-aminopyrazol-1-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione 23

5-Methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione (0.165 g, 0.89 mmol) was added to a solution of 1,5-diamino-3-*tert*-butylpyrazole **12** (0.154 g, 1 mmol) in acetonitrile (2 cm^3). The mixture was left stirring overnight. A white precipitate was isolated and was identified as *5-(3-tert-butyl-5-aminopyrazol-1-ylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione* **23** (0.115 g, 37%), mp 230–231 °C (from acetonitrile). (Found: C, 54.25; H, 6.45; N, 17.9. $C_{14}H_{20}N_4O_4$ requires C, 54.55; H, 6.5; N, 18.2%); δ_H (^{2}[H]$_6$DMSO) 11.45 (1H, br d, $^3J_{H,NH}$ 14.6) 8.57 (1H, d, $^3J_{H,NH}$ 14.6), 6.55 (1H, s), 6.37 (2H, br s), 1.70 (6H, s) and 1.25 (9H, s); δ_C (^{2}[H]$_6$DMSO) 164.58 (quat), 162.27 (quat), 156.83 (quat), 152.21, 136.99 (quat), 104.69 (quat), 87.51 (quat), 87.11, 32.16 (quat), 30.21 (CH_3) and 26.57 (CH_3); *m/z* 308 (M^+, 18%), 251 (20), 250 (100), 217 (16), 205 (15), 204 (79), 191 (20) and 123 (11).

6-*tert*-Butyl-2-(methylthio)pyrazolo[1,5-*b*]1,2,4-triazole 26

1,5-Diamino-3-*tert*-butylpyrazole **12** (0.60 g, 3.9 mmol) was dissolved in methanol (10 cm^3). Water (0.3 cm^3) was then added followed by potassium hydroxide (0.27 g, 4.82 mmol) and carbon disulfide (2.55 cm^3). The mixture was heated to reflux for 2–3 h during which time the solution became yellow and evolution of hydrogen sulfide was noted. The mixture was then neutralised with hydrochloric acid (5%), poured into water and extracted with ethyl acetate (2 × 25 cm^3). The organic layer was separated and dried over anhydrous magnesium sulfate. On removal of solvent *in vacuo* a semi-solid product was obtained. TLC showed many products had formed but NMR spectroscopy showed a peak at δ_H 5.45 which was attributable to 6-*tert*-butylpyrazolo[1,5-*b*]1,2,4-triazole-2-thione **25** which was used without further purification.

The solid mixture was dissolved in methanol (10 cm^3), iodomethane (0.22 cm^3, 3.53 mmol) was added followed by potassium hydroxide (0.2 g, 3.57 mmol). The mixture was stirred at room temperature for 2 h, evaporated to dryness and partitioned between hydrochloric acid (5%) and ethyl acetate. The organic layer was dried over magnesium sulfate to give an oily product. TLC showed the presence of product as a purple spot on spraying with developer **22** and aqueous potassium persulfate. The mixture was purified by column chromatography (silica), [ethyl acetate–light petroleum (bp 60–80 °C) (50 : 50) eluents] to give a yellow solid, *6-tert-butyl-2-(methylthio)-pyrazolo[1,5-b]1,2,4-triazole* **26** (0.045 g, 5.5%), mp 226–227 °C (from ethyl acetate). (Found: C, 50.05; H, 6.6; N, 25.6. $C_9H_{14}N_4S$ 0.33 H_2O requires C, 50.0; H, 6.8; N, 25.9%); δ_H (^{2}[H]$_6$DMSO) 12.77 (1H, br, s), 5.61 (1H, s), 2.61 (3H, s) and 1.26 (9H, s); δ_C (^{2}[H]$_6$DMSO) 161.43 (quat), 147.64 (quat), 138.01 (quat), 74.81, 32.49 (quat), 30.54 (CH_3) and 14.84 (CH_3); *m/z* 210 (M^+, 81%), 195 (100), 168 (20), 148 (32) and 127 (23).

6-*tert*-Butyl-2-methylthio-7-(4-diethylamino-2-methylphenylimino)pyrazolo[1,5-*b*]1,2,4-triazole 28

6-*tert*-Butyl-2-(methylthio)pyrazolo[1,5-*b*]1,2,4-triazole **26** (0.052 g, 0.25 mmol) was dissolved in a mixture of 5% aqueous sodium carbonate solution (5 cm^3) and methanol (2.5 cm^3). The developer, 4-(*N,N*-diethylamino)-3-methylaminobenzene hydrochloride **27** (0.062 g, 0.29 mmol) was added, followed by potassium persulfate (0.15 g, 0.55 mmol). The solution became intense purple and the resulting dye, *6-tert-butyl-2-methylthio-7-(4-diethylamino-2-methylphenylimino)-7H-pyrazolo[1,5-b]-1,2,4-triazole* **28** was formed as a purple precipitate, (0.077 g, 81%), mp 133–134 °C (crude). (Found: M^+ 384.2097. $C_{20}H_{28}N_6S$ requires *M* 384.2096); λ_{max} (MeOH), 558 nm, λ_{max} (EtOAc), 546 nm, λ_{max} (cyclohexane), 524 nm; ε(EtOH) 58 400; δ_H 9.02 (1H, d, ^3J 9.4), 6.73 (1H, d, d, ^3J 9.4 and ^4J 2.9), 6.59 (1H, d, ^4J 2.9), 3.49 (4H, q, ^3J 7.1), 2.66 (3H, s), 2.53 (3H, s), 1.53 (9H, s) and 1.25 (6H, t, ^3J 7.1); δ_C 170.23 (quat), 162.30 (quat), 151.84 (quat), 146.70 (quat), 143.09 (quat), 135.21 (quat), 131.12 (quat), 127.10, 112.54, 110.39, 44.92, 35.38 (quat), 29.43, 20.42, 14.98 and 12.73; *m/z* 384 (M^+, 100%), 369 (33) and 258 (24).

7-*tert*-Butyl-2,3-dimethylpyrazolo[1,5-*b*]1,2,4-triazine 29

1,5-Diamino-3-*tert*-butylpyrazole **12** (0.154 g, 1 mmol) was dissolved in acetic acid (5 cm^3). Butanedione (0.086 g, 1 mmol) was added and the mixture was heated under reflux for 1 h. The solvent was removed *in vacuo* and the residue was partitioned between hexane (25 cm^3) and aqueous sodium bicarbonate (25 cm^3). The organic layer was dried ($MgSO_4$) and the solvent was removed at reduced pressure to give *7-tert-butyl-2,3-dimethylpyrazolo[1,5-b]-1,2,4-triazine* **29** (0.110 g, 54%), mp 144–145 °C (from ethanol–cyclohexane). (Found: M^+ 204.1367. $C_{11}H_{16}N_4$ requires *M* 204.1375); δ_H 6.37 (1H, s), 2.50 (3H, s), 2.48 (3H, s) and 1.34 (9H, s); δ_C 164.32 (quat), 150.62 (quat), 144.42 (quat), 140.57 (quat), 91.37, 32.60 (quat), 30.12 (CH_3), 22.52 (CH_3) and 19.44 (CH_3); *m/z* 204 (M^+, 51%), 189 (100), 162 (28), 148 (67), 109 (11) and 77 (13).

7-*tert*-Butyl-2,3-diphenylpyrazolo[1,5-*b*]1,2,4-triazine 30

1,5-Diamino-3-*tert*-butylpyrazole **12** (0.15 g, 1 mmol) was reacted with benzil (0.50 g, 4.2 mmol) in acetic acid (5 cm^3). The resulting solution was heated to reflux for 4 h. The solvent was removed and the residue was purified by column chromatography on silica (toluene eluent), to give a yellow solid, *7-tert-butyl-2,3-diphenylpyrazolo[1,5-b]1,2,4-triazine* **30** (0.090 g,

27%), mp 135–136 °C (from hexane–ethanol). (Found: M^+ 328.1678. $C_{21}H_{20}N_4$ requires *M* 328.1688); δ_H 7.43–7.25 (10H, m), 6.67 (1H, s) and 1.46 (9H, s); δ_C 166.59 (quat), 149.98 (quat), 145.69 (quat), 140.67 (quat), 136.76 (quat), 134.67 (quat), 129.59, 129.42, 129.33, 129.11, 128.10 (2C), 92.93, 32.94 (quat) and 30.17 (CH_3); *m*/*z* 328 (M^+, 100%), 313 (65), 286 (26), 211 (12), 210 (78), 178 (12), 105 (11) and 77(55).

1*H*-8-*tert*-Butyl-2,4-dimethylpyrazolo[1,5-*b*]1,2,4-triazepine 31

A solution of 1,5-diamino-3-*tert*-butylpyrazole **12** (0.20 g, 1.3 mmol) and acetylacetone (0.13 g, 1.3 mmol) in acetic acid (4 cm^3) was heated under reflux for 2 h. The solvent was removed *in vacuo* to yield a semi-solid product. This was washed with aqueous sodium carbonate to remove the last traces of acetic acid. The mixture was purified by column chromatography (alumina) using a 30 : 70 mixture of ethyl acetate–hexane as eluant. The dark red oily product obtained was identified as *1H-8-tert-butyl-2,4-dimethylpyrazolo[1,5-b]-1,2,4-triazepine* **31** (0.11 g, 39%), bp 120–122 °C (0.2 Torr). (Found: M^+ 218.1529. $C_{12}H_{18}N_4$ requires *M* 218.1531); δ_H 6.12 (1H, s), 3.18 (2H, s), 2.30 (3H, s), 2.26 (3H, s) and 1.31 (9H, s); δ_C 161.23 (quat), 160.07 (quat), 154.46 (quat), 135.70 (quat), 97.62, 42.33, 32.74 (quat), 30.76, 28.56 and 24.70; *m*/*z* 218 (M^+, 57%), 217 (17), 203 (100), 189 (6), 176 (13), 164 (14), 163 (10), 162 (13) and 148 (14).

1*H*-8-*tert*-Butyl-4-methylpyrazolo[1,5-*b*]1,2,4-triazepin-2(3*H*)-one 33

A solution of 1,5-diamino-3-*tert*-butylpyrazole **12** (0.82 g, 5.33 mmol) and ethyl acetoacetate (0.70 g, 5.40 mmol) in acetic acid (8 cm^3) was heated under reflux for 1 h. The solvent was removed *in vacuo* and the residue was washed with ether to yield a pale buff coloured solid, *1H-8-tert-butyl-4-methylpyrazolo-[1,5-b]1,2,4-triazepin-2(3H)-one* **33** (0.51 g, 44%), mp 221–222 °C (from ethyl acetate). (Found: C, 59.6; H, 7.15; N, 24.85. $C_{11}H_{16}N_4O{\cdot}0.1H_2O$ requires C, 59.5; H, 7.3; N, 25.25%); δ_H 9.96 (1H, br, s), 5.80 (1H, s), 3.36 (2H, s), 2.32 (3H, s) and 1.28 (9H, s); δ_C 165.66 (quat), 160.12 (quat), 157.53 (quat), 132.61 (quat), 90.56, 41.73, 32.17 (quat), 29.92 and 24.44; *m*/*z* 220 (M^+, 51%), 205 (100), 178 (15) and 164 (11).

1*H*-8-*tert*-Butyl-3,4-dimethylpyrazolo[1,5-*b*]1,2,4-triazepin-2(3*H*)-one 34

A solution of 1,5-diamino-3-*tert*-butylpyrazole **12** (0.171 g, 1.11 mmol) and ethyl 2-methylacetoacetate (0.160 g, 1.11 mmol) in acetic acid (3 cm^3) was heated under reflux for 1.5 h. The solvent was removed *in vacuo* to yield initially an oil. Trituration with ether gave a buff solid, *1H-8-tert-butyl-3,4-di-methylpyrazolo[1,5-b]1,2,4-triazepin-2(3H)-one* **34** (0.144 g, 55%), mp 204–205 °C (from ethanol–cyclohexane). (Found: M^+ 234.1487. $C_{12}H_{18}N_4O$ requires *M* 234.1480); δ_H 5.80 (1H, s), 3.45 (1H, q, ^3J 6.9), 2.21 (3H, s), 1.42 (3H, d, ^3J 6.9) and 1.30 (9H, s); δ_C 167.28 (quat), 162.00 (quat), 160.34 (quat), 132.91 (quat), 90.04, 42.49, 32.20 (quat), 29.95, 19.79, and 10.53; *m*/*z* 234 (M^+, 42%), 219 (100), 178 (9) and 96 (11).

1*H*-8-*tert*-Butyl-4-propylpyrazolo[1,5-*b*]1,2,4-triazepin-2(3*H*)-one 35

A solution of 1,5-diamino-3-*tert*-butylpyrazole **12** (0.184 g, 1.2 mmol) and ethyl butyrylacetate (0.189 g, 1.2 mmol) in acetic acid (5 cm^3) was heated under reflux for 1.5 h. Removal of solvent *in vacuo* yielded a yellow oil which crystallised over a period of 2 days. The solid was washed with cyclohexane to give *1H-8-tert-butyl-4-propylpyrazolo[1,5-b]1,2,4-triazepin-2(3H)-one* **35** (0.125 g, 42%), mp 155–156 °C (from ethanol–cyclohexane). (Found: M^+ 248.1648. $C_{13}H_{20}N_4O$ requires *M* 248.1637); δ_H 5.80 (1H, s), 3.34 (2H, s), 2.59–2.51 (2H, m), 1.76–1.65 (2H, m), 1.28 (9H, s) and 0.98–0.91 (3H, m); δ_C 165.84 (quat), 160.39 (quat), 160.16 (quat), 132.79 (quat), 90.52, 40.68, 40.05, 32.17 (quat), 29.93, 18.84, and 13.42; *m*/*z* 248 (M^+, 46%), 233 (100), 220 (18), 206 (10), 164 (14) and 124 (14).

1*H*-8-*tert*-Butyl-9-chloro-4-methylpyrazolo[1,5-*b*]1,2,4-triazepin-2(3*H*)-one 36

A solution of 1,5-diamino-3-*tert*-butyl-4-chloropyrazole **15** (0.212 g, 1.12 mmol) and ethyl acetoacetate (0.146 g, 1.12 mmol) in acetic acid (8 cm^3) was heated under reflux for 1 h. Removal of solvent gave an oil which crystallised on cooling in a salt–ice bath. The solid was washed with light petroleum (bp 60–80 °C) and was identified as *1H-8-tert-butyl-9-chloro-4-methylpyrazolo[1,5-b]1,2,4-triazepin-2(3H)-one* **36** (0.232 g, 81%), mp 224–225 °C (from cyclohexane–ethanol). (Found: M^+ 254.0939. $C_{11}H_{15}{}^{35}ClN_4O$ requires *M* 254.0934); δ_H 3.36 (2H, s), 2.31 (3H, s) and 1.35 (9H, s); δ_C 164.71 (quat), 158.72 (quat), 153.65 (quat), 130.03 (quat), 94.20 (quat), 42.02, 33.00 (quat), 28.17 and 24.52; *m*/*z* 256 (M^+, 20%), 254 (M^+, 60%), 241 (32), 239 (100), 214 (10), 212 (30), 177 (10) and 158 (10).

Reaction of 1,5-diamino-3-*tert*-butylpyrazole with other β-dicarbonyl compounds

Reaction of solutions of 1,5-diamino-3-*tert*-butylpyrazole (1 mmol) in acetic acid (3 cm^3) with ethyl benzoylacetate (1 mmol), with ethyl pivaloylacetate (1 mmol) or with diethyl malonate (1 mmol) at reflux for 1.5–2 h gave oils which were identified as starting material, though with some decomposition.

7-*tert*-Butyl-3-methylpyrazolo[1,5-*b*]1,2,4-triazin-2-one 42

A solution of 1,5-diamino-3-*tert*-butylpyrazole **12** (1.0 g, 6.5 mmol) and ethyl (or methyl) pyruvate (1.5 g, 13 mmol) was heated under reflux in acetic acid solution (10 cm^3) for 1.5 h. The solvent was then removed under reduced pressure. The residue was washed with ether and filtered to obtain *7-tert-butyl-3-methylpyrazolo[1,5-b]1,2,4-triazin-2-one* **42** as a white solid, (0.42 g, 32%), mp 233–234 °C (from ethanol–cyclohexane). (Found: C, 58.2; H, 6.85; N, 27.2. $C_{10}H_{14}N_4O$ requires C, 58.25; H, 6.85; N, 27.2%); δ_H 5.86 (1H, s), 2.41 (3H, s) and 1.33 (9H, s); δ_C 162.87 (quat), 154.29 (quat), 145.95 (quat), 132.98 (quat), 84.17, 32.57 (quat), 29.89 (CH_3) and 16.92 (CH_3); *m*/*z* 206 (M^+, 47%), 191 (100), 164 (26) and 150 (53).

7-*tert*-Butyl-8-chloro-3-methylpyrazolo[1,5-*b*]1,2,4-triazin-2-one 43

A solution of 1,5-diamino-3-*tert*-butyl-4-chloropyrazole **15** (0.8 g, 4.25 mmol) and ethyl pyruvate (0.5 g, 4.30 mmol) was heated under reflux in acetic acid solution (7 cm^3) for 1.5 h. The solvent was then removed *in vacuo*, the residue was washed with light petroleum (bp 60–80 °C) to yield a white solid *7-tert-butyl-8-chloro-3-methylpyrazolo[1,5-b]1,2,4-triazin-2-one* **43** (0.74 g, 72%), mp 174–175 °C (from ethanol–cyclohexane). (Found: M^+ 240.0770. $C_{10}H_{13}{}^{35}ClN_4O$ requires M^+ 240.0778); δ_H 7.66 (1H, br, s), 2.40 (3H, s) and 1.14 (9H, s); δ_C 156.42 (quat), 153.35 (quat), 147.24 (quat), 130.60 (quat), 88.01 (quat), 33.40 (quat), 33.40 (CH_3) and 16.82 (CH_3); *m*/*z* 242 (M^+, 20%), 240 (M^+, 60%), 227 (33), 225 (100), 215 (5), 200 (15), 198 (45), 186 (25), 184 (76), 163 (25) and 156 (40).

Crystal data for 33

$C_{11}H_{16}N_4O$, $M = 220.28$, monoclinic, $a = 10.483(5)$, $b = 9.356(4)$, $c = 12.297(3)$ Å, $\beta = 101.14(3)°$, $U = 1183.4(8)$ Å^3, $T = 298(2)$ K, space group $P2_1/a$ (Alt. $P2_1/c$, No. 14), $Z = 4$, $D_c = 1.237$ g cm^{-3}, μ(Mo–$K\alpha$) = 0.084 mm^{-1}, 1554 unique reflections measured and used in all calculations. Final R_1 [869 $F > 4\sigma(F)$] = 0.0570 and wR(all F^2) was 0.171.

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