Investigations of the Richter reaction in a series of vicinal alkynylpyrazolediazonium salts

Eugene V. Tretyakov,[a] David W. Knight[b] and Sergei F. Vasilevsky *[a]

[a] *Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, 630090, Novosibirsk, Russian Federation*
[b] *Chemistry Department, Cardiff University, PO Box 912, Cardiff, UK CF10 3TB*

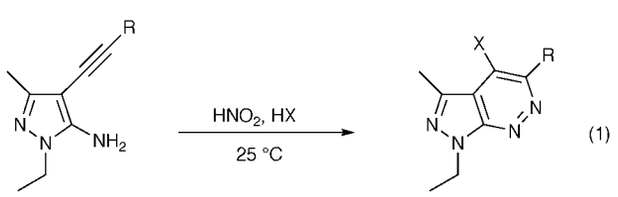
Received (in Cambridge, UK) 11th May 1999, Accepted 23rd September 1999

All positional isomers of *vic*-alkynylaminopyrazoles, when treated with sodium nitrite in hydrochloric or hydrobromic acid, are transformed into pyrazolopyridazines *via* cyclisation of the corresponding alkynylpyrazolyldiazonium salts. The ease of cyclisation was found to depend markedly on the position of the alkynyl and diazonium groups around the pyrazole nucleus: 4-alkynylpyrazole-5-diazonium salts derived from the corresponding 4-alkynyl-5-aminopyrazoles **1a**–**c** cyclized at 0–20 °C to 4-chloro- and 4-bromo-1*H*-pyrazolo-[3,4-*c*]pyridazines **2a**–**c** and **3a**; the heterocyclization of 5-alkynylpyrazole-4-diazonium salts **5a**,**b** required heating to 100–105 °C and gave 7-chloro-1*H*-pyrazolo[4,3-*c*]pyridazines **6a**,**b** in good yield. The cyclisation of 1-methyl-3-alkynylpyrazole-4-diazonium salts **8a**,**b** was accompanied by methyl group migration towards the neighbouring nitrogen atom to give the same 7-chloro-1*H*-pyrazolo[4,3-*c*]pyridazines **6a**,**b** arising from cyclisation of the 5-alkynylpyrazole-4-diazonium salts **5a**,**b**. When treated with sodium hydrogen carbonate, the 1,5-dimethylpyrazol-4-diazonium salts **8a**–**c** gave the 5-(pyrazol-4-ylazomethyl)pyrazole-4-diazonium chloride derivatives **9a**–**c** which cyclized in the presence of base to give the corresponding 6-(pyrazol-4-ylazo)-4*H*-pyrazolo[4,3-*c*]pyrazoles **10a**–**c**.

In contrast, the heterocyclization of 4-alkynylpyrazole-3-diazonium salts derived from 4-alkynyl-3-aminopyrazoles **11a**,**b** at 50–60 °C gave 4-hydroxy-2*H*-pyrazolo[3,4-*c*]pyridazines **12a**,**b** as the major components together with the corresponding 6-halogeno-pyridazines **13a**,**b** and **14a** as minor components.

Heterocyclization of vicinally functionalized aromatic acetylenic compounds has recently become increasingly important as a method for the synthesis of fused heterocyclic systems. However, this type of heterocyclization of acetylenic derivatives of pyrazolediazonium salts is virtually unknown. We reasoned that it could be possible to prepare multinuclear heterocyclic compounds which are difficult to obtain by other methods using this strategy. In previous communications,[1,2] we have demonstrated that the classical Richter reaction,[3] the intramolecular cyclisation of 2-alkenyl- or alkynyl-aryldiazonium salts to give cinnolines, can be applied to the synthesis of not only 4-hydroxy- but also 4-bromo- and 4-chlorocinnolines. Attempting to extend the applicability of this reaction, we have found that the behaviour of alkynylpyrazolediazonium chlorides differs from that of their benzene analogues. Thus, cyclisation of 1,3-dimethyl-5-phenylethynylpyrazole-4-diazonium salts does not lead to the expected 4-hydroxydiazines[4] and, under similar conditions, the isomeric 1,5-dimethyl-3-phenylethynylpyrazole-4-diazonium chloride does not even react *via* a Richter mechanism.[4] In general, it is difficult to predict the outcome of cyclisations of alkynylpyrazolediazonium salts, even with closely related arrangements of functional groups since reaction can occur at both the α- and β-carbon atoms of the acetylenic substituent. Moreover, it is known that the electrophilicity of the diazo group and the nucleophilicity of a triple bond depend markedly on their positions around the pyrazole ring and that this can affect both the course and ease of cyclisation and even its viability.[5] Hence, we have undertaken a comprehensive study of such heterocyclisations of diazotized vicinal alkynylaminopyrazoles, the full details of which we report herein.

In the first examples, diazotization of the 4-alkynyl-5-amino-3-methyl-1-ethylpyrazoles **1a**–**c** in hydrochloric or hydrobromic acid at −15 °C led to the corresponding alkynylpyrazolediazonium salts which underwent facile cyclisation upon warming to



1 2,3

1-3 **a** R = Ph; **b** R = 4-MeOC$_6$H$_4$; **c** R = (CH$_2$)$_5$CH$_3$

2a-c X = Cl; **3a** X = Br

25–30 °C to give fair to good yields of the 4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*c*]pyridazines **2a**–**c** and the corresponding 4-bromo derivative **3a** respectively [reaction (1)]. In contrast, the isomeric 5-alkynylpyrazole-4-diazonium chlorides **5a**,**b** cyclized only after heating to 100–105 °C for 2 hours, to give good yields of the 1,3-dimethyl-7-chloro-1*H*-pyrazolo[4,3-*c*]pyridazines **6a**,**b** (Scheme 1).

3-Alkynylpyrazole-4-diazonium chlorides **8a**,**b** derived from the corresponding aminopyrazoles **7a**,**b** underwent cyclisation much more slowly than the isomeric derivatives **5a**,**b** (concentrated HCl, 100–105 °C, 6 h) (Scheme 2). To our surprise, the reaction products were identical to compounds **6a**,**b** formed by cyclisation of diazotized amines **4a**,**b**. Thus, the cyclisation of pyrazole-4-diazonium chlorides **8a**,**b** causes methyl group migration to the neighbouring nitrogen atom. A small yield of the diazonium salt **9a** was also isolated.

The behaviour of aminopyrazole **7c** under these conditions was quite different; diazotization using nitrous acid in concentrated hydrochloric acid gave rise to an alkynylpyrazolediazonium chloride which did not participate in the Richter reaction, probably due to the electron-withdrawing effect of the nitro group. Instead, after neutralization of the hydrochloric acid

with sodium hydrogen carbonate, the methyl group at position 5 of the pyrazole added to the diazonium group of a second molecule of the diazotized pyrazole. The resulting diazonium chloride **9c** was cyclized in pyridine at 110 °C to give the pyrazolo[4,3-*c*]pyrazole **10c**. Because of the much lower reactivity of the diazonium salt **8a**, with respect to Richter cyclisation, the same sequence could also be carried out starting with aminopyrazole **7a**. The azodiazonium salt **9a** was thus obtained by sequential diazotization and neutralization of the diazotizing mixture at 5–10 °C. It is interesting that alkynylpyrazole-diazonium salt **9a**, compared to pyrazole-4-diazonium chloride **8a**, does not undergo a Richter reaction. However, the salt **9a** could be smoothly cyclized in boiling ethanol in the presence of triethylamine to give the pyrazolo[4,3-*c*]pyrazole **10a**.

It is of interest that, unlike the 1,5-dimethylpyrazole-4-diazonium chlorides **8**, cyclisations of 5-benzylpyrazole-4-diazonium chlorides occur intramolecularly under the same conditions. Thus, reduction of either 5-benzyl-1-methyl-3-phenyl-4-phenylazopyrazole or 1-phenyl derivatives by sodium dithionite, diazotization of the resulting amines and subsequent treatment with sodium hydrogen carbonate resulted in formation of 1-methyl-3,6-diphenyl- and 1,3,6-triphenyl-1,4-dihydropyrazolo[4,3-*c*]pyrazole, respectively (Fig. 1).[6] We have established that, in the absence of an arylethynyl group, interaction between the 5-methyl and 4-diazonium groups occurs intermolecularly. Thus, azopyrazole **9d** was synthesized by diazotization of 4-amino-1,5-dimethylpyrazole **7d** and subsequent intermolecular condensation of the resulting diazonium chloride **8d**, after neutralization using sodium hydrogen carbonate at 5–10 °C. Azopyrazole **9d** also underwent cyclisation in boiling ethanol in the presence of piperidine to give the pyrazolopyridazine **10d**.

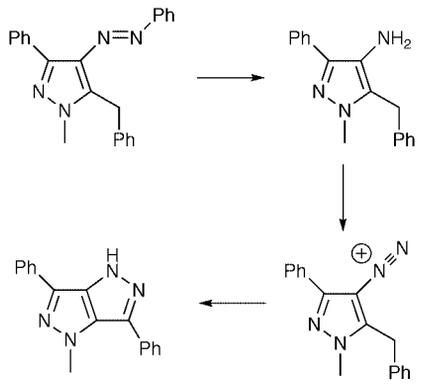
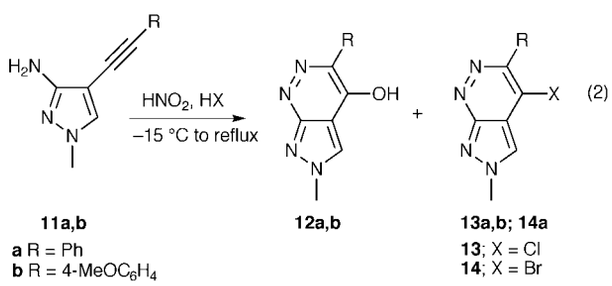


Fig. 1

To create a complete pattern of transformations of aminoacetylenes of the pyrazole series in the Richter reaction, we have studied the cyclisations of 4-alkynylpyrazole-3-diazonium salts containing no methyl groups at position 5 of the heterocycle, thus excluding the possibility of intermolecular condensations between these and the diazonium functions. 4-Alkynyl-3-aminopyrazoles **11a**,**b** were diazotized under standard conditions. Heating the resulting alkynylpyrazole-diazonium salts in the diazotization solution at 50–60 °C caused cyclisation, to give mainly the 5-substituted-4-hydroxy-2-methyl-2*H*-pyrazolo[3,4-*c*]pyridazines **12a**,**b** together with the 6-chloro derivatives **13a**,**b** as minor components [reaction (2)].



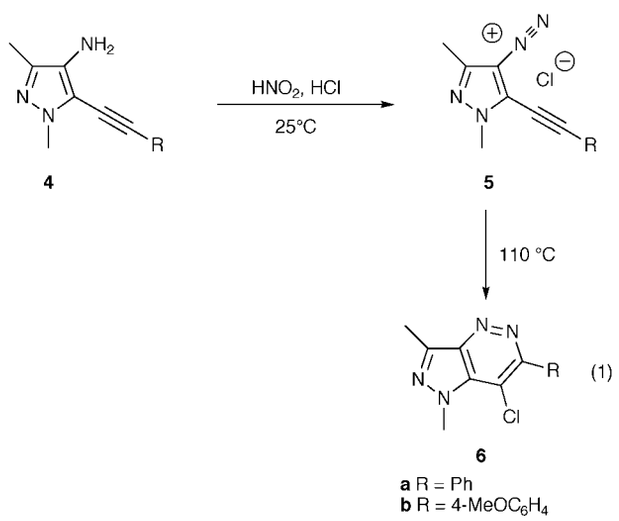
11a,b
a R = Ph
b R = 4-MeOC$_6$H$_4$

12a,b

13a,b; 14a
13; X = Cl
14; X = Br

(2)

Similarly, diazotization of amine **11a** using hydrobromic acid led to a low yield of the corresponding bromide **14a**. To confirm the structure of the pyrazolopyridazine **12a**, we performed an



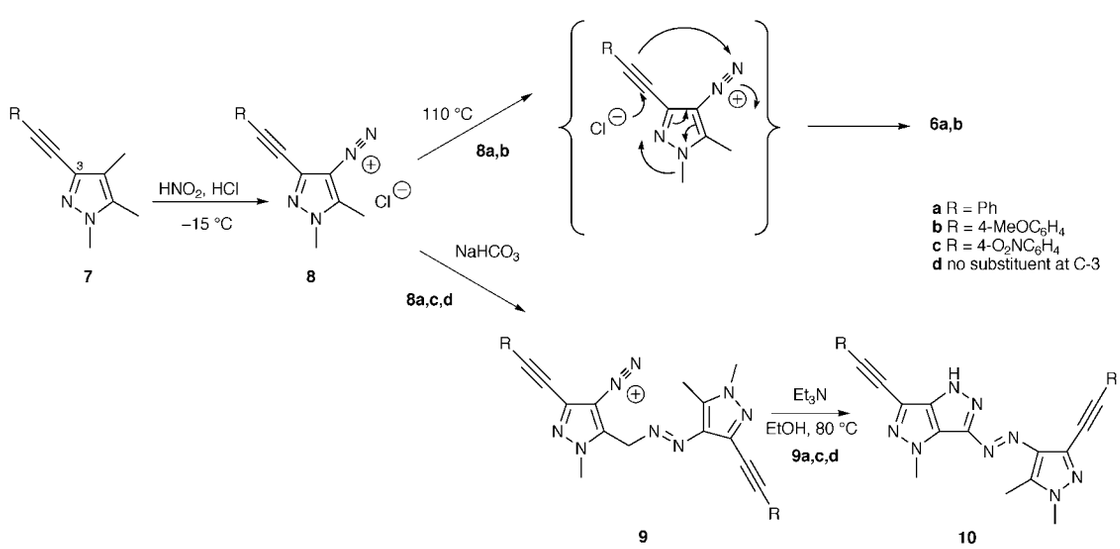
4

5

6
a R = Ph
b R = 4-MeOC$_6$H$_4$

(1)

Scheme 1



7

8

8a,c,d

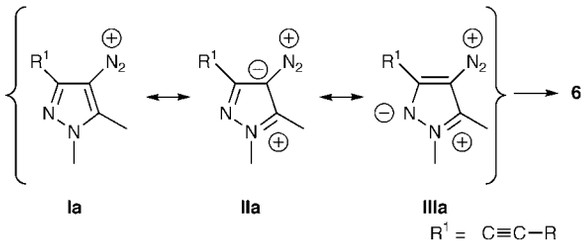
6a,b

a R = Ph
b R = 4-MeOC$_6$H$_4$
c R = 4-O$_2$NC$_6$H$_4$
d no substituent at C-3

9

10

Scheme 2



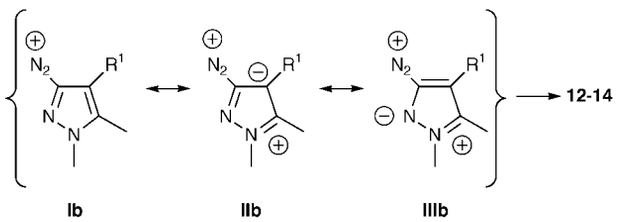
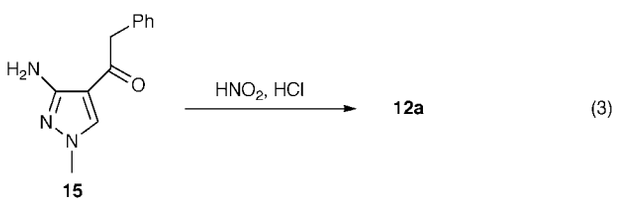


Fig. 2



alternative synthesis of this compound by diazotization of 4-phenylacetyl-3-amino-1-methylpyrazole **15** and obtained a product identical to compound **12a** [reaction (3)] produced by cyclisation of amine **11a**. However, taking into account a possible migration of the methyl group to the neighbouring nitrogen atom, compounds **12a**,**b** could in fact be the related 1*H*-pyrazolo[3,4-*c*]pyridazines. Additional evidence that the products **12a**,**b** were indeed 2*H*-pyrazolo[3,4-*c*]pyridazines was obtained as follows: it was found that, under the action of phosphorus oxychloride (80 °C, 10 min), the pyridazines **12a**,**b** are transformed almost quantitatively into the corresponding chloro derivatives **13a**,**b**. Upon heating in concentrated hydrochloric acid (95–100 °C, 2 h), these were completely hydrolyzed back to the parent 2*H*-pyrazolo[3,4-*c*]pyridazines **12a**,**b**, whereas 4-chloro-1,3-dimethyl-5-phenyl-1*H*-pyrazolo[3,4-*c*]pyridazine[2] does not undergo this reaction. It is concluded that cyclisation of the diazotized aminopyrazoles **11a**,**b** conserves the structure of the pyrazole ring and leads to the formation of 2*H*-pyrazolo[3,4-*c*]pyridazines **12** and **13**. However, cyclisation of diazonium salts derived from aminopyrazoles **7a**,**b** is followed by methyl group migration to the neighbouring nitrogen atom.

The difference in behaviour of 3-alkynylpyrazole-4- and 4-alkynylpyrazole-3-diazonium salts [**Ia** and **Ib** respectively] upon Richter synthesis may be explained as follows (Fig. 2). The cyclisation is assumed to be favoured by the aromaticity inherent in the newly-formed pyridazine ring. In some cases, however, as for example upon cyclisation of *vic*-alkenyl- and *vic*-alkynyldiazonium salts, the cyclic conjugated polyene is not formed at the initial stage of the reaction. In these cases, the aromaticity[7] of the transition state, arising from disrotatory electrocyclic cyclisation may compensate for the energy losses upon approach of the reaction centres. Obviously, these considerations may be extended to the cyclisation of *vic*-alkynylarenediazonium salts because in the disrotatory process, the overlapping of orbitals in the ring plane is reached earlier than the π-overlapping of p-orbitals of both the nitrogen β-atom of the diazonium group and the β-carbon atom of the triple bond. At the same time, the electrocyclic reactions of *vic*-acetylenic derivatives of monocyclic arenediazonium salts may formally be realised by a second mechanism, *via* the 6-electron 1,6-

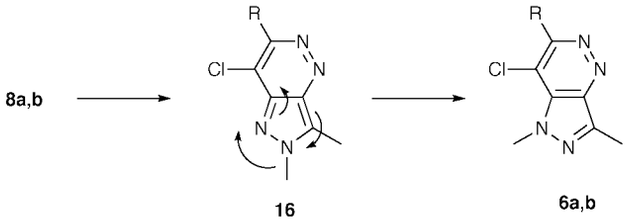


Fig. 3

electrocyclic mechanism involving the entire aromatic cycle system. In the former case, the energy of the transition state must be lower due to a higher level of aromaticity. In examples of the cyclisation of 3-alkynylpyrazole-4- and 4-alkynylpyrazole-3-diazonium salts **Ib**, a peculiarity of these substrates is the possibility that cyclisation *via* a 1,6-electrocyclic reaction, depends upon the degree of double-bond character of the bond between carbon atoms in positions 3 and 4 which, in turn, is determined by the contribution of resonance structures **IIIa**,**b** to the true structure of the pyrazolediazonium salts. Due to the introduction of an electron-acceptor diazonium group into position 4 of the ring, the contribution of resonance structures **IIa** and **IIIa** is large, when compared to the contribution of structures **IIb** and **IIIb** to the true structure of the corresponding diazonium salts. The difference is, probably, in the fact that in the first case, the distribution of electron density favours the methyl cation migration towards the neighbouring nitrogen atom. The unexpected [1,2]-methyl shift encountered in the cyclisation of diazonium salts **8a**,**b** may feature the intermediacy of initial structures **16**, related to isoindoles, which then rearrange as indicated (Fig. 3) to give the more stable products **6a**,**b**, related to indoles.

Thus, the Richter reaction of the series of alkynylaminopyrazoles opens up a route to halo-derivatives of 1*H*-pyrazolo[3,4-*c*]pyridazines, 2*H*-pyrazolo[3,4-*c*]pyridazines and 1*H*-pyrazolo[4,3-*c*]pyridazines. By studying the heterocyclization of 3-alkynyl-5-methylpyrazole-4-diazonium chlorides, we have uncovered the formation of the products of intermolecular interaction between methyl and diazonium groups which made it possible to develop a method for producing new azopolypyrazole compounds: 5-(pyrazol-4-ylazomethyl)-pyrazole-4-diazonium chlorides and 6-(pyrazol-4-ylazo)-1,4-dihydro-pyrazolo[4,3-*c*]pyrazoles.

Experimental

General details

Phosphorus oxychloride was freshly distilled. Other commercial reagents were used without further purification. Alkynylaminopyrazoles were synthesized according to our procedure.[8] Silica gel "KSK" (Russia, 100–200 mesh, air dried) was used for column chromatography. ^{1}H NMR spectra were recorded using a JEOL FX-90Q and Bruker 400 spectrometers at room temperature and locked to the deuterium resonance of the solvent ($CDCl_3$). The chemical shifts were calculated relative to the solvent signal using as internal standard δ_H 7.24 ppm. IR spectra were obtained on a UR-20 spectrophotometer. Melting points were determined with a Kofler apparatus. All organic solutions from work-ups were dried by brief exposure to anhydrous magnesium sulfate followed by filtration. Solvents were removed by rotary evaporation.

4-Chloro-1-ethyl-3-methyl-5-phenyl-1*H*-pyrazolo[3,4-*c*]pyridazine 2a

A solution of sodium nitrite (0.35 g, 5.1 mmol) in water (3 mL) was added dropwise to a stirred suspension of aminopyrazole **1a** (1.05 g, 4.7 mmol) in 36% aqueous hydrochloric acid (40 mL), maintained at −15 °C. The mixture was stirred without

further cooling for 1 h then neutralized with concentrated aqueous sodium hydrogen carbonate and extracted with chloroform (3 × 20 ml). The combined extracts were dried, the solvent evaporated and the residue chromatographed on a neutral Al_2O_3 column with chloroform as the eluant to give the *pyridazine* **2a** (0.81 g; 64%) as colourless crystals, mp 88–89 °C (from hexane–benzene); δ_H 1.62 (3H, t, *J* 7.2, CH_2CH_3), 2.84 (3H, s, 3-CH_3), 4.76 (2H, q, *J* 7.2, CH_2CH_3), 7.45–7.60 (3H, m, 3′-, 4′- and 5′-H) and 7.80 (2H, dd, *J* 7.6 and 2.1, 2′- and 6′-H) [Found: C, 61.13; H, 4.89; Cl, 12.92. $C_{14}H_{13}ClN_4$ requires C, 61.65; H, 4.80; Cl, 13.00%].

4-Chloro-1-ethyl-3-methyl-5-(4-methoxyphenyl)-1*H*-pyrazolo-[3,4-*c*]pyridazine 2b

Aminopyrazole **1b** (0.90 g, 3.5 mmol) was diazotized in exactly the same manner as the foregoing to give, after preparative TLC on silica gel (elution with chloroform), the *pyridazine* **2b** (0.51 g, 47.8%) as yellowish crystals, mp 106–107 °C (benzene–hexane); δ_H 1.61 (3H, t, *J* 7.2, CH_2CH_3), 2.79 (3H, s, 3-CH_3), 3.82 (3H, s, OCH_3), 4.73 (2H, q, *J* 7.2, CH_2CH_3), 7.06 (2H, d, *J* 8.6, 3′- and 5′-H) and 7.74 (2H, d, *J* 8.6, 2′- and 6′-H) [Found: C, 59.89; H, 4.89; Cl, 11.92. $C_{15}H_{15}ClN_4O$ requires C, 59.50; H, 4.99; Cl, 11.71%].

4-Chloro-1-ethyl-5-hexyl-3-methyl-1*H*-pyrazolo[3,4-*c*]pyridazine 2c

Following the foregoing procedure, diazotization of aminopyrazole **1c** (2.33 g, 10 mmol) and purified by preparative TLC on silica gel (20:1 chloroform–acetone) gave the *pyridazine* **2c** (2.30 g, 82%) as a colourless oil; δ_H 0.90 (3H, t, *J* 8.1, $(CH_2)_5CH_3$), 1.20–1.50 (8H, m, 4 × CH_2), 1.55 (3H, t, *J* 7.5, CH_3CH_2N), 2.70 (3H, s, 3-CH_3), 3.25 (2H, t, *J* 7.5, CH_2) and 4.65 (2H, q, *J* 7.5, CH_2N) [Found: C, 59.36; H, 7.71; Cl, 12.02. $C_{14}H_{21}ClN_4$ requires C, 59.88; H, 7.54; Cl, 12.63%].

4-Bromo-1-ethyl-3-methyl-5-phenyl-1*H*-pyrazolo[3,4-*c*]pyridazine 3a

A solution of sodium nitrite (0.35 g, 5.1 mmol) in water (3 ml) was added dropwise at −15 °C to a stirred suspension of aminopyrazole **1a** (1.05 g, 5.0 mmol) in 47% aqueous hydrobromic acid (40 ml). The resulting mixture was stirred at 25–28 °C for 1 h. After the usual work up, preparative thin-layer chromatography (5:1 chloroform–acetone) gave the *bromopyridazine* **3a** (1.16 g, 77%), mp 97–98 °C (1:1 benzene–hexane); δ_H 1.60 (3H, t, *J* 7.3, CH_2CH_3), 2.68 (3H, s, 3-CH_3), 4.60 (2H, q, *J* 7.3, CH_2N), 7.40–7.61 (3H, m, 3′-, 4′- and 5′-H) and 7.74 (2H, dd, *J* 7.6 and 2.2, 2’- and 6′-H) [Found: C, 53.46; H, 4.03; Br, 25.29. $C_{14}H_{13}BrN_4$ requires C, 53.16; H, 4.13; Br, 25.19%].

7-Chloro-1,3-dimethyl-6-phenyl-1*H*-pyrazolo[4,3-*c*]pyridazine 6a

a) A solution of sodium nitrite (0.35 g, 5.1 mmol) in water (5 ml) was added dropwise at −10 °C to a stirred suspension of the 4-aminopyrazole **4a** (0.90 g, 4.3 mmol) in 36% aqueous hydrochloric acid (50 ml). The mixture was stirred at ambient temperature for 1 h then heated to boiling point and allowed to reflux for 2 h. The cooled reaction mixture was poured into water (50 ml), neutralized with sodium hydrogen carbonate and extracted with chloroform (3 × 70 ml). The combined extracts were passed through silica gel (3 cm in length). The filtrate was concentrated at reduced pressure to give 0.90 g (82%) of the title compound as brown crystals. Recrystallization of the crude product from benzene–hexane (1:1) gave an analytical sample of the *pyridazine* **6a** as yellow crystals, mp 175–176 °C; δ_H 2.97 (3H, s, 3-CH_3), 4.28 (3H, s, 1-CH_3), 7.45–7.61 (3H, m, 3′-, 4′- and 5′-H) and 7.90 (2H, dd, *J* 7.8 and 2.2, 2′- and 6′-H) [Found: C, 60.23; H, 4.28; Cl, 13.43. $C_{13}H_{11}ClN_4$ requires C, 60.35; H, 4.29; Cl, 13.70%].

b) A solution of sodium nitrite (0.07 g, 1.0 mmol) in water (1 ml) was added dropwise at −15 °C to a stirred suspension of pyrazole **7a** (0.20 g, 0.95 mmol) in 36% aqueous hydrochloric acid (40 ml). The resulting mixture was stirred at ambient temperature for 1 h then heated to boiling point and allowed to reflux for 6 h. The cooled solution was neutralized with concentrated aqueous sodium hydrogen carbonate and extracted with chloroform (3 × 20 ml). The combined extracts were dried and concentrated. Preparative thin-layer chromatography (5:1 chloroform–acetone) of the residue yielded a high R_f fraction (0.12 g, 65%) which was identical with pyridazine **6a** prepared by method a). The low R_f fraction contained 0.04 g (16%) of the diazonium chloride **9a** (see below).

7-Chloro-1,3-dimethyl-6-(4-methoxyphenyl)-1*H*-pyrazolo[4,3-*c*]-pyridazine 6b

The pyridazine **6b** was similarly prepared by the two forgoing methods: using method a), pyrazole **4b** (0.90 g, 3.7 mmol) was converted into **6b** (0.82 g, 76%) while reaction of pyrazole **7b** (0.90 g, 3.7 mmol) under conditions b) gave **6b** (0.69 g, 64%). The *pyridazine* **6b**, yellow crystals, mp 186–187 °C (benzene–hexane) showed δ_H 2.91 (3H, s, 3-CH_3), 3.87 (3H, s, OCH_3), 4.11 (3H, s, 1-CH_3), 7.21 (2H, d, *J* 8.5, 3′- and 5′-H) and 7.98 (2H, d, *J* 8.5, 2′- and 6′-H) [Found: C, 58.59; H, 4.69; Cl, 11.88. $C_{14}H_{13}ClN_4O$ requires C, 58.23; H, 4.54; Cl, 12.28%].

1-Methyl-5-(1,5-dimethyl-3-phenylethynylpyrazolyl-4-azomethyl)-3-phenylethynylpyrazole-4-diazonium chloride 9a

A solution of sodium nitrite (0.50 g, 7.2 mmol) in water (2 ml) was added dropwise at 0 °C to a stirred suspension of aminopyrazole **7a** (1.05 g, 4.9 mmol) in 36% aqueous hydrochloric acid (10 ml) and the resulting mixture stirred at 30–45 °C for 2 h. The solution was neutralized with solid sodium hydrogen carbonate, stirred at 20–25 °C for 4 h, then diluted with water (50 ml). The resulting yellow solid was filtered off, washed with water (5 ml) and dried in a vacuum desiccator over phosphorus pentoxide to give the *diazonium salt* **9a** (1.18 g, 92%); ν_{max}/cm^{-1} (KBr) 2340 (NN) and 2230 (CC) [Found: C, 59.34; H, 3.72; Cl, 13.78. $C_{26}H_{21}ClN_8 \cdot HCl$ requires C, 60.34; H, 4.29; Cl, 13.70%].

1-Methyl-5-(1,5-dimethylpyrazol-4-ylazomethyl)pyrazole-4-diazonium chloride 9d

By the foregoing procedure, aminopyrazole **7d** (1.94 g, 1.7 mmol) was diazotized at 0 °C. The work up described for salt **9a** provided 2.25 g (86.2%) of the *diazonium salt* **9d**; ν_{max}/cm^{-1} (KBr) 2300 (NN). [Found: C, 40.11; H, 4.27; Cl, 18.48. $C_{10}H_{13}ClN_8 \cdot 0.5HCl$ requires C, 40.18; H, 4.55; Cl, 17.79%].

1-Methyl-6-(1,5-dimethyl-3-phenylethynylpyrazol-4-ylazo)-3-phenylethynyl-1,4-dihydro-pyrazolo[4,3-*c*]pyrazole 10a

A stirred suspension of diazonium salt **9a** (0.50 g, 0.97 mmol) and triethylamine (10 ml) in ethanol (100 ml) was refluxed for 25 min, by which time the salt had dissolved. The cooled reaction mixture was evaporated to 5 ml and diluted with ether (30 ml). The resulting brown precipitate was filtered off, washed with water (20 ml), dried in a vacuum desiccator over potassium hydroxide and recrystallised from chloroform and benzene to afford yellow crystals of *azo compound* **10a**. Subsequent chromatography of the product on an alumina column (20 × 100 mm, elution with chloroform) provide an analytical sample of **10a** (0.23 g, 54%), mp 246–247 °C; ν_{max}/cm^{-1} (KBr) 3400 (NH) and 2230 (CC); δ_H 2.66 (3H, s, 5-CH_3), 3.88 (3H, s, N-CH_3), 4.45 (3H, s, N-CH_3), 7.30–7.41 (6H, m, Ph) and 7.51–7.63 (4H, m, Ph) [Found: C, 70.02; H, 4.49; N, 25.34. $C_{26}H_{20}N_8$ requires C, 70.26; H, 4.53; N, 25.21%].

1-Methyl-6-[1,5-dimethyl-3-(4-nitrophenylethynyl)pyrazol-4-ylazo]-3-(4-nitrophenylethynyl)-1,4-dihydro-pyrazolo[4,3-*c*]-pyrazole 10c

A solution of sodium nitrite (0.30 g, 7.2 mmol) in water (1 ml) was added dropwise at −5 °C to a stirred suspension of aminopyrazole **7c** (0.26 g, 1.0 mmol) in 36% aqueous hydrochloric acid (10 ml) and the resulting mixture stirred at 30–45 °C for 0.5 h. The solution was then neutralized with sodium carbonate, stirred at 20–25 °C for 12 h, and finally quenched with water (50 ml). The resulting orange solid was filtered off, washed with water (5 ml) and dried in a vacuum desiccator over phosphorus pentoxide. The crude diazonium salt **9c** was refluxed in pyridine (30 ml) until a homogeneous solution was obtained (40 min). After cooling, the resulting mixture was stored at ambient temperature for 14 h. The resulting brown precipitate was filtered off, washed with 3% aqueous hydrochloric acid (15 ml) and water. Crystallization of the crude product from pyridine [3 times (with activated charcoal)] gave the azo compound **10c** (0.21 g, 77%) as a yellow powder, mp 349–356 °C (decomp.); ν_{max}/cm^{-1} (KBr) 3400 (NH), 2225 (CC), 2215, 1520 (NO_2) and 1340 [Found: C, 56.52; H, 3.65; N, 25.35. $C_{26}H_{18}N_{10}O_4$ requires C, 56.34; H, 3.74; N, 25.16%].

1-Methyl-6-(1,5-dimethylpyrazol-4-ylazo)-1,4-dihydro-pyrazolo[4,3-*c*]pyrazole 10d

A stirred suspension of diazonium salt **9d** (0.50 g, 1.7 mmol) and pyridine (1 ml) in ethanol (50 ml) was refluxed for 2 h until the diazonium salt dissolved. Work up as for the foregoing azo compound **10a** gave the *product* **10d** (0.35 g, 86%) as yellow crystals, mp 265–266 °C (chloroform); ν_{max}/cm^{-1} (KBr) 3400 (NH); δ_H 2.60 (3H, s, 5-CH_3), 3.85 (3H, s, N-CH_3), 4.26 (3H, s, N-CH_3), 7.39 (1H, s, NCH) and 7.94 (1H, s, NCH); *m*/*z* 244 [M$^+$] [Found: C, 48.85; H, 4.98. $C_{10}H_{12}N_8$ requires C, 49.07; H, 4.95%].

6-Hydroxy-1-methyl-5-phenyl-2*H*-pyrazolo[3,4-*c*]pyridazine 12a

a) A solution of sodium nitrite (0.35 g, 5.1 mmol) in water (2 ml) was added dropwise at −10 °C to a stirred suspension of aminopyrazole **11a** (0.90 g, 4.6 mmol) in 36% aqueous hydrochloric acid (40 ml) and the resulting mixture refluxed for 3 h. The cooled mixture was diluted with water (100 ml) and neutralized with solid sodium hydrogen carbonate. The resulting yellowish precipitate was filtered off, washed with water (5 ml) and purified by crystallization from dioxane (3×) to give an analytical sample of the *hydroxypyridazine* **12a** (0.94 g, 91%) as colourless crystals, mp 273–274 °C; ν_{max}/cm^{-1} (KBr) 3560 (OH), 3480 (NH) and 1635; δ_H 4.10 (3H, s, N-CH_3), 7.42–7.67 (5H, m, Ph) and 8.13 (1H, s, 7-H) [Found: C, 62.46; H, 4.45. $C_{12}H_{10}N_4O$ requires C, 63.71; H, 4.46%].

b) A suspension of the chloropyridazine **13a** (0.50 g, 2.0 mmol) in 36% aqueous hydrochloric acid (20 ml) was stirred at 100–105 °C for 1 h. Work up as described in a) gave the title *product* **12a** (0.41 g, 89%) which exhibited spectroscopic and analytical data identical to the foregoing sample.

c) The hydroxy pyridazine **12a** (0.07 g, 90%) was also prepared from corresponding bromodiazine **14a** (0.10 g, 0.35 mmol) by method b). The product again showed identical data to that displayed by the product from method a).

d) A solution of sodium nitrite (0.05 g, 0.72 mmol) in water (1 ml) was added dropwise at −10 °C to a stirred suspension of the acylpyrazole **15** (0.10 g, 0.47 mmol) in 36% aqueous hydrochloric acid (10 ml) and the resulting mixture stirred at 100–105 °C for 4 h. The cooled mixture was diluted with water (40 ml), neutralized with sodium hydrogen carbonate and extracted with chloroform (5 × 50 ml). The combined extracts were treated with sodium sulfate, the suspension heated to boiling point, filtered, and concentrated at reduced pressure to give the crude product as yellow crystals. Preparative thin-layer chromatography (5:1 chloroform–acetone) provided 0.04 g (38%) of product **12a**, identical with that obtained from **11a** by method a).

4-Hydroxy-2-methyl-5-(4-methoxyphenyl)-2*H*-pyrazolo[3,4-*c*]-pyridazine 12b

A solution of sodium nitrite (0.35 g, 5.1 mmol) in water (2 ml) was added dropwise at −15 °C to a stirred suspension of aminopyrazole **11b** (0.80 g, 3.5 mmol) in 36% aqueous hydrochloric acid (40 ml). The reaction mixture was refluxed for 1 h, then cooled, diluted with water (100 ml) and neutralized with solid sodium hydrogen carbonate. The resulting yellowish precipitate was filtered off, washed with water (5 ml) and purified by recrystallization from dioxane (3×) to give the *hydroxypyridazine* **12b** (0.76 g, 84%) as colourless crystals, mp 284–285 °C; ν_{max}/cm^{-1} (KBr) 3490, 3620 and 1630; δ_H 3.95 (3H, s, OCH_3), 4.15 (3H, s, N-CH_3), 7.03 (2H, d, *J* 8.6, 2′- and 6′-H), 7.40 (2H, d, *J* 8.6, 3′- and 5′-H) and 7.90 (1H, s, 7-H) [Found: C, 60.93; H, 4.72. $C_{13}H_{12}N_4O_2$ requires C, 60.13; H, 4.81%].

4-Hydroxy-2-methyl-5-phenyl-2*H*-pyrazolo[3,4-*c*]pyridazine 12a and 4-chloro-2-methyl-5-phenyl-2*H*-pyrazolo[3,4-*c*]pyridazine 13a

a) A solution of sodium nitrite (0.35 g, 5.1 mmol) in water (3 ml) was added dropwise at −15 °C to a stirred suspension of pyrazole **11a** (0.57 g, 4.3 mmol) in 36% aqueous hydrochloric acid (20 ml) and the resulting mixture stirred at 50–60 °C for 2 h. The cooled solution was neutralized with concentrated aqueous sodium hydrogen carbonate and the resulting suspension extracted with benzene (2 × 50 ml). The combined benzene extracts were filtered, as was the aqueous layer, to give a white solid. This crude product was washed with water (5 ml), dried and recrystallised twice from dioxane to afford an analytical sample of the *hydroxypyridazine* **12a** (0.51 g, 74%), which exhibited spectroscopic and analytical data identical to that recorded below. The benzene solution was dried and evaporated and the residue chromatographed on silica gel (chloroform) to afford 0.015 g (1.9%) of the *chloropyridazine* **13a**, mp 247–248 °C (chloroform); δ_H 4.42 (3H, s, 1-CH_3), 7.43–7.58 (3H, m, 3′-, 4′- and 5′-H), 7.75–7.88 (2H, m, 2′- and 6′-H) and 8.20 (1H, s, 7-H); *m*/*z* 247.0 [M$^+$(Cl^{37}) + H, 3%], 245.9 [M$^+$(Cl^{37}), 24], 244.9 [M$^+$(Cl^{35}) + H, 10], 243.9 [M$^+$(Cl^{35}), 68], 208.9 (68) [M − Cl] [Found: C, 58.00; H, 3.55; Cl, 14.14. $C_{12}H_9ClN_4$ requires C, 57.91; H, 3.55; Cl, 14.49%].

b) Phosphorus oxychloride (1 ml) was added to a stirred solution of pyrazolopyridazine **12a** (0.25 g, 1.5 mmol) in dioxane (10 ml) at 0 °C. The resulting mixture was heated to boiling and allowed to reflux for 5 min, then cooled to room temperature, quenched with water (50 ml) and neutralized with solid sodium hydrogen carbonate. The precipitated yellow solid was filtered off, washed with water (5 ml) and purified by column chromatography on silica gel (chloroform) to afford the *chloropyridazine* **13a** as yellowish crystals (0.22 g, 79%), mp 247–248 °C, which displayed spectroscopic and analytical data identical to the foregoing sample.

4-Chloro-2-methyl-5-(4-methoxyphenyl)-2*H*-pyrazolo[3,4-*c*]-pyridazine 13b

A mixture of the hydroxypyridazine **12b** (0.17 g, 0.66 mmol) and phosphorus oxychloride (0.5 ml) in dioxane (10 ml) was heated to reflux for 10 min, by which time the starting material had all reacted, according to TLC analysis. The mixture was cooled to room temperature, diluted with water (30 ml) and neutralized with concentrated aqueous sodium hydrogen carbonate. The resulting mixture was extracted with chloroform (3 × 20 ml) and the combined extracts dried and evaporated to give *chloropyrazolo[3,4-c]pyridazine* **13b** as a yellowish solid. The

crude product was chromatographed on a silica gel column (10 : 1 chloroform–acetone) followed by recrystallization from carbon tetrachloride to give an analytical sample of **13b** (0.13 g, 71%) as colourless crystals, mp 258–259 °C; δ_H 3.90 (3H, s, OCH_3), 4.42 (3H, s, N-CH_3), 7.04 (2H, d, *J* 8.7, 2′- and 6′-H), 7.75 (2H, d, *J* 8.7, 3′- and 5′-H) and 8.15 (1H, s, 7-H) [Found: C, 59.89; H, 4.89; Cl, 11.92. $C_{13}H_{11}ClN_4O$ requires C, 59.50; H, 4.99; Cl, 11.71%].

4-Bromo-2-methyl-5-phenyl-2*H*-pyrazolo[3,4-*c*]pyridazine 14a

A solution of sodium nitrite (0.36 g, 5.2 mmol) in water (2 ml) was added dropwise to a stirred suspension of aminopyrazole **11a** (0.42 g, 3.2 mmol) in 47% aqueous hydrobromic acid (20 ml) at −15 °C. The mixture was stirred at 25–28 °C for 3 h. After the workup described for the chloropyridazine **13a**, the crude product was chromatographed on silica gel (chloroform), followed by recrystallization from benzene and hexane (1 : 1 v/v) to give the *bromopyridazine* **14a** (0.06 g, 8.4%) as yellowish crystals, mp 256–257 °C (chloroform); δ_H 4.12 (3H, s, N-CH_3), 7.46–7.68 (5H, m, Ph) and 8.15 (1H, s, 7-H); *m*/*z* 290.9 [$M^+(Br^{81})$ + H, 2%], 289.9 [$M^+(Br^{81})$, 14], 288.9 [$M^+(Br^{79})$ + H, 2], 287.9 [$M^+(Br^{79})$] and 208 [M^+ − Br, 68].

References

1 S. F. Vasilevsky, E. V. Tretyakov and H. D. Verkruijsse, *Synth. Commun.*, 1994, **24**, 1733.
2 S. F. Vasilevsky and E. V. Tretyakov, *Liebigs Ann. Chem.*, 1995, 775; *Heterocycl. Commun.*, 1998, **4**, 519.
3 A. E. A. Porter, in *Comprehensive Organic Chemistry*, ed, D. Barton and W. D. Ollis, Volume 4, Pergamon Press, Oxford, 1979.
4 E. V. Tretyakov and S. F. Vasilevsky, *Mendeleev Commun.*, 1996, 190.
5 S. F. Vasilevsky, T. V. Anisimova and M. S. Shvartsberg, *Bull. Acad. Sci. USSR*, *Div. Chem. Sci.*, 1983, 626.
6 J. M. Lee, A. Matsumoto, M. Yoshida and O. Simamura, *Bull. Chem. Soc Jpn.*, 1974, **47**, 1039.
7 M. J. S. Dewar and R. C. Dougherty, *The PMO Theory of Organic Chemistry*, Plenum Press, New York, 1975.
8 E. V. Tretyakov, D. W, Knight and S. F. Vasilevsky, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 3713.

Paper 9/03755A