Peculiarities of copper(I)- and palladium-catalyzed cross-coupling of terminal alkynes with vicinal amino- and (*N*-acetylamino)-iodopyrazoles. Synthesis of alkynylaminopyrazoles

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A number of vicinal amino- and (*N*-acetylamino)-alkylpyrazoles have been synthesized by cross-coupling reactions of iodopyrazoles with alk-1-ynes using a combination of $Pd(PPh_3)_2Cl_2$ and CuI as catalyst in Et_3N or with copper acetylides. The latter Stephens–Castro reaction of copper acetylides with these amino- and (*N*-acetylamino)-iodopyrazoles was established as a common method for the preparation of (*N*-acetylamino)alkynylpyrazoles. The Pd/Cu-catalyzed cross-coupling of iodopyrazoles (Sonogashira reaction) with alk-1-ynes bearing electron-releasing substituents was unsuitable for the synthesis of alkynylpyrazoles: 3- and 5-iodopyrazoles were unreactive but, in the case of 4-iodo derivatives, reductive deiodination, accompanied by homocoupling of the alk-1-yne component, was the only reaction.

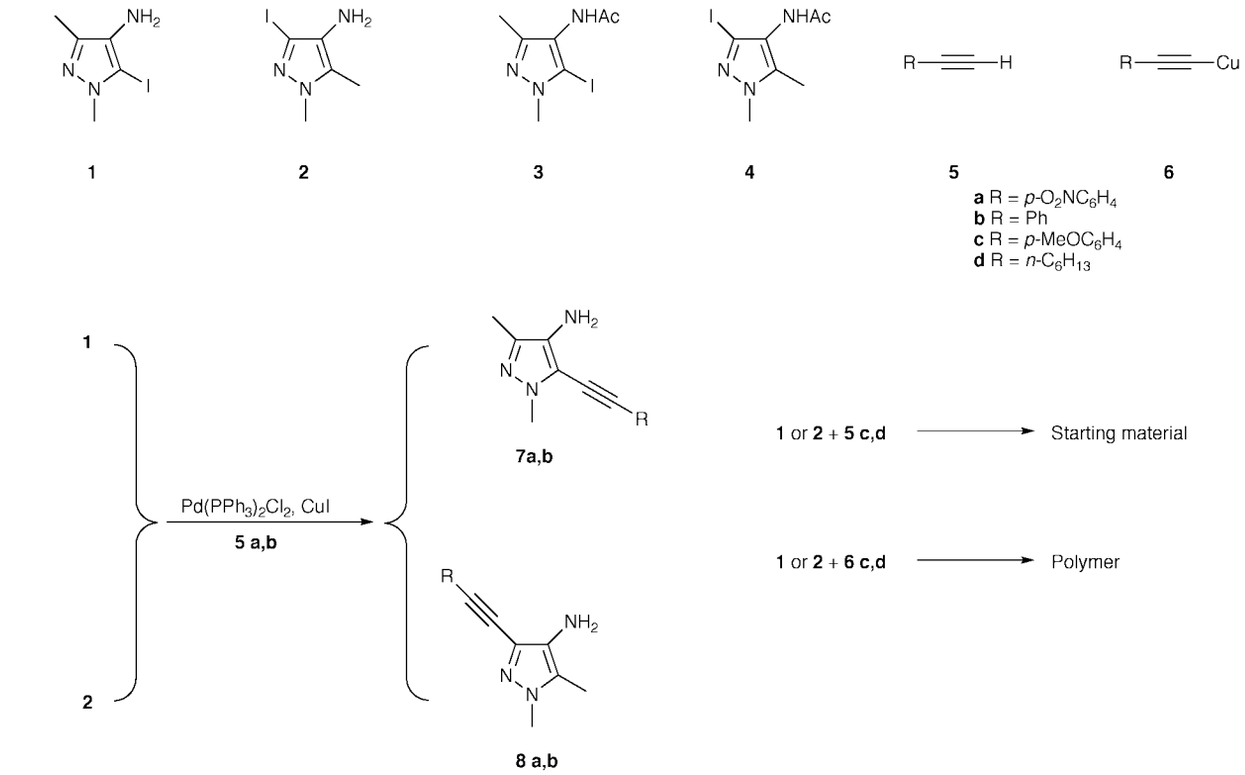
The intramolecular cyclisation of *o*-alkynylaryl diazonium salts, the von Richter reaction, is a very useful method for the construction of ring fused pyridazines, such as cinnolines from *o*-alkynylanilines, which can be applied to the construction of a wide variety of polyheterocyclic systems. Comparison between such thermal cyclizations of vicinal alkynylbenzene and some alkynylpyrazole diazonium salts has revealed significant differences in the behaviour of these classes of compounds,[1,2] probably due to the distinct differences in the π-electron densities of the benzene and pyrazole rings. We have therefore performed syntheses of vicinal aminoalkynylpyrazoles with all possible variations of the arrangement of the relevant functional groups (*i.e.* alkynyl and amino), in order to fully investigate these differences in behaviour and to determine the synthetic utility of the Richter cyclisation of *vic*-alkynylpyrazolediazonium salts. As far as we are aware, there is little information available[3] regarding the synthesis of vicinal aminoalkynylpyrazoles and hence we report herein on the outcome of these studies.

An attractive method for obtaining the target *vic*-amino-alkynylpyrazoles appeared to be by Sonogashira coupling[4] of the known aminoiodopyrazoles[5] with terminal acetylenes. Both 3- and 5-iodo derivatives underwent successful coupling with alk-1-ynes using the catalyst system $Pd(PPh_3)_2Cl_2$–CuI in hot triethylamine under an argon atmosphere. Thus, reactions of iodoaminopyrazoles **1** and **2** with either *p*-nitrophenyl- or phenyl-acetylene **5a** and **5b** were complete within 0.5–4 h at 80 °C, depending on the acetylene reactivity, and gave the alkynylaminopyrazoles **7a**,**b** and **8a**,**b** in moderate to good yields (Scheme 1). However, attempts to carry out similar couplings between iodoaminopyrazoles **1** and **2** with more electron-rich alk-1-ynes, specifically *p*-methoxyphenylacetylene **5c** and oct-1-yne **5d**, under the same conditions but for 40 h, were unsuccessful; up to 76% of the starting iodopyrazoles was returned. We hoped that these difficulties could be overcome by applying the alternative Stephens–Castro reaction[6] of pre-formed copper acetylides to obtain alkynylaminopyrazoles **7c**,**d** and **8c**,**d**. However, reactions between iodopyrazoles **1** and **2** and the copper acetylides **6c** and **6d** in refluxing pyridine[6] gave a large number of products and much intractable polymer. These complications were avoided by protection of the amino-pyrazoles as the corresponding *N*-acetyl derivatives. The resulting (*N*-acetylamino)iodopyrazoles **3** and **4** coupled smoothly with the copper acetylides **6b–d** in pyridine at 110–115 °C (Scheme 2). The reactions required 4–10 h for completion; for comparison, a similar coupling of iodobenzene with copper phenylacetylide required 10 h at 115 °C.[6] The resulting (*N*-acetylamino)alkynylpyrazoles **9b–d** and **10b–d** were cleanly hydrolysed to the target aminopyrazoles **7b–d** and **8b–d** using sodium hydroxide in refluxing aqueous ethanol.

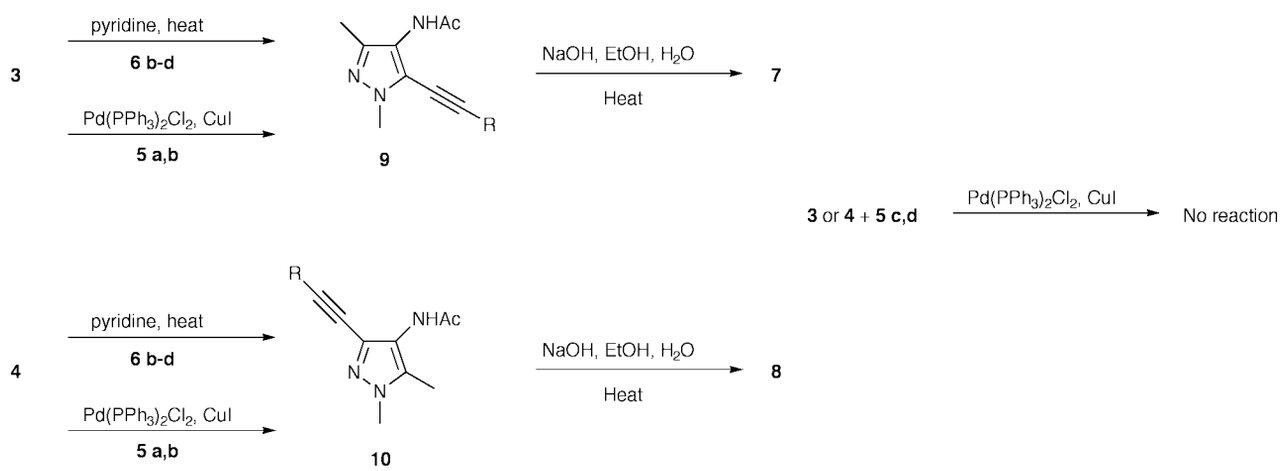
As the work-up procedure required for the copper acetylide version of the coupling reactions was considerably less convenient when compared to the palladium-catalysed method and taking into account the fact that the acetyl group reduced the deactivating influence of the amino group, we tried to synthesize the same alkynylpyrazoles **9a–d** and **10a–d** using the latter palladium–copper catalytic system.[5] However, iodopyrazoles **3** and **4** did not react with alkynes **5c** and **5d** in the presence of $Pd(PPh_3)_2Cl_2$ and CuI in boiling triethylamine. Only introduction of the more reactive terminal alkynes **5a** and **5b** into (*N*-acetylamino)iodopyrazoles **3** and **4** gave the target alkynylpyrazoles **9a**,**b** and **10a**,**b** under these conditions.

Thus, the rate and viability of Pd-catalyzed couplings between 4-aminoiodopyrazoles and alk-1-ynes depends upon the electronic character of the acetylenic substituent and an approximate criterion for choosing the method of coupling is the acidity of the alk-1-yne component.[7] It is concluded that terminal alkynes with $pK_a < 29$ (CH-acidity of phenylacetylene) were able to undergo Sonogashira couplings using the $Pd(PPh_3)_2Cl_2$–CuI–Et_3N system with derivatives of 3- and 5-aminoiodopyrazoles. The same iodopyrazoles with less acidic alkynes ($pK_a > 29$) however require the use of the copper acetylide method and, for maximized yields, acetylation of the amino group.

Taking into consideration this conclusion and also the lower reactivity of the iodine atom in 4-iodopyrazoles,[8] only cross-couplings with *N*-acetylated amino-4-iodopyrazoles were examined. Iodopyrazoles **11** and **12** were coupled with *p*-nitrophenylacetylene **5a** in Et_3N in the presence of $Pd(PPh_3)_2Cl_2$ and CuI at 80 °C to give good yields of the *N*-acetyl-4-alkynylpyrazoles **13a** and **14a** (Scheme 3). However, attempts to couple

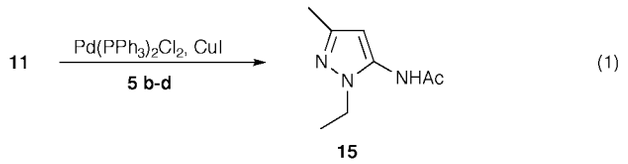


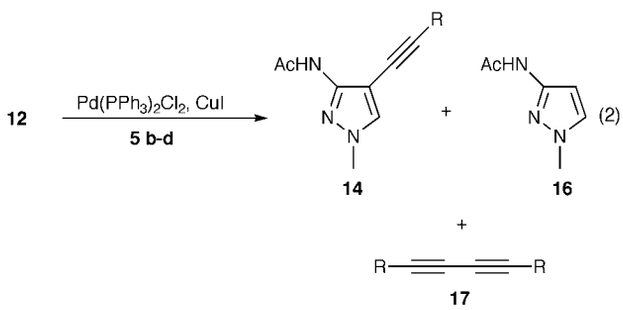
Scheme 1



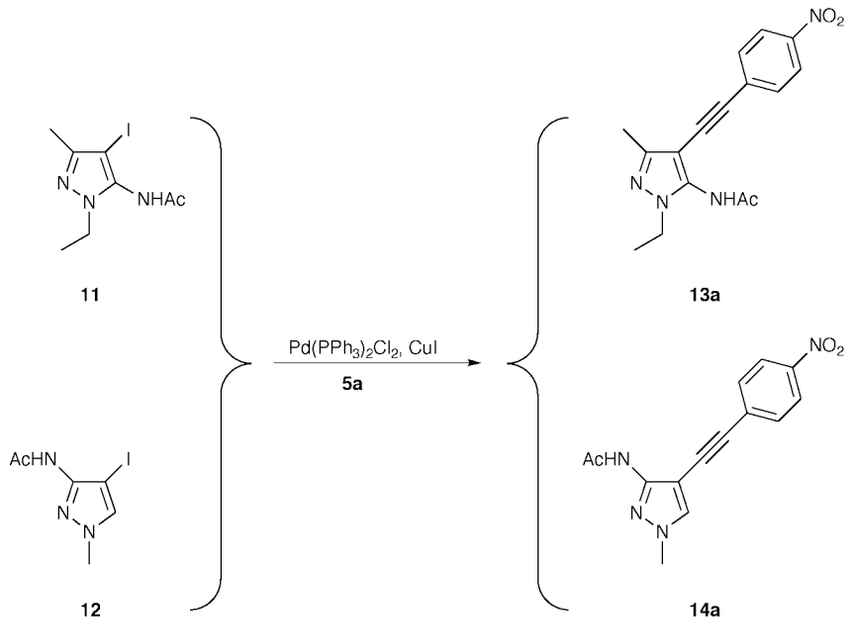
Scheme 2

(*N*-acetyl)-4-iodopyrazole **11** under the same conditions with alkynes **5b–d**, once again, were unsuccessful; instead, reductive deiodination to give 5-(*N*-acetylamino)-3-methyl-1-ethylpyrazole **15** occurred [reaction (1)]. However, the isomeric 3-(*N*-acetylamino)pyrazole **12** was somewhat less inclined to deiodination. Thus, the Pd/Cu-catalyzed cross-coupling of iodopyrazole **12** and phenylacetylene **5b** gave 3-(*N*-acetylamino)-1-methyl-4-phenylethynylpyrazole **14b** and 3-(*N*-acetylamino)-1-methylpyrazole **16** in isolated yields of 56 and 26%, respectively [reaction (2)]. In similar reactions with acetylenes **5c** and **5d**, deiodination dominated. The yields of *N*-acetylaminopyrazole **16** in these cases reached 88% (Table 1).





Therefore, the Pd/Cu-catalyzed cross-coupling of acetylenes with 3- and 5-(*N*-acetylamino)-4-iodopyrazoles was complicated by reductive deiodination. According to the generally accepted mechanism, this catalytic cross-coupling involves initial reaction of the pre-catalyst and copper acetylide with the formation of bis(triphenylphosphine)dialkynylpalladium(II), which decomposes to give bis(triphenylphosphine)palladium(0) and the "dimeric" acetylene.[11] In such reactions, the homo-



Scheme 3

Table 1 Catalytic synthesis of acetylenylpyrazoles

Substrates	Time/h	Product (yield, %)[a]	Diacetylene (yield, %)[a]
1 + **5a**	0.5	**7a** (71)	—
1 + **5b**	6	**7b** (86)	—
2 + **5a**	1.5	**8a** (73)	—
2 + **5b**	8	**8b** (36)	—
3 + **5a**	0.5	**9a** (88)	—
3 + **5b**	2	**9b** (71)	—
4 + **5a**	1.5	**10a** (73)	—
4 + **5b**	4	**10b** (91)	—
1–**4** + **5c** or **5d**	10–26	[b]	—
11 + **5a**	5.5	**13a** (63)	—
11 + **5b**	3	**15** (81)[c,d]	**17b** (93)[e]
11 + **5c**	5	**15** (86)[c]	**17c** (72)[f]
11 + **5d**	12	**15** (78)[c]	**17d** (49)[g]
12 + **5a**	6	**14a** (58)	—
12 + **5b**	4	**14b** (56)[h]	**17b** (18)[e]
12 + **5c**	4	**16** (88)[i]	**17c** (91)[f]
12 + **5d**	6	**16** (70)[i]	**17d** (38)[g]

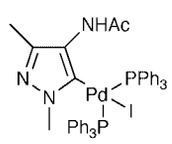
[a] Yields are based on iodopyrazoles. [b] Up to 76% if the initial compound was returned. [c] Compound **11** gave 5-(*N*-acetylamino)-1-ethyl-3-methylpyrazole **15** (see Experimental section). [d] Effect of different conditions on the condensation: (i) with the molar ratio of the components PzI/PhC≡CH/CuI/$Pd(PPh_3)_2Cl_2$ = 1.0 : 1.0 : 1.0 : cat., alkynylpyrazole **13b** was isolated in 41% yield; (ii) PzI/PhC : CH/CuI/$Pd(PPh_3)_3Cl_2$ = 1.0 : 0.0 : cat. : cat.—gave iodopyrazole **11** (74%). [e] Diphenylbutadiyne showed identical spectral data to that published earlier.[9] [f] Mp 148–149 °C (benzene); δ_H ($CDCl_3$) 3.95 (6H, s, 2 × OCH_3), 6.88 (4H, d, *J* 9, 3-, 5-, 3′- and 5′-H) and 7.65 (4H, d, *J* 9, 2-, 6-, 2′- and 6′-H). [g] Hexadeca-7,9-diyne showed analytical data identical with that published earlier.[10] [h] Compound **16** was also isolated in 26% yield. [i] Compound **12** gave 3-(*N*-acetylamino)-1-methylpyrazole **16**, mp 97–98 °C (benzene–hexane); ν_{max}/cm^{-1} ($CHCl_3$) 3420 (NH) and 1705 (C=O); δ_H ($CDCl_3$) 2.65 (3H, s, $COCH_3$), 3.80 (3H, s, N-CH_3), 6.00 (1H, br s, NH), 6.43 (1H, s, 4-H) and 7.32 (1H, s, 5-H) [Found: C, 51.81; H, 6.57; N, 30.42. $C_6H_9N_3O$ requires C, 51.79; H, 6.52; N, 30.20%].

coupled product is formed in amounts corresponding to the quantity of the pre-catalyst used.

In line with this, we found that, in all cases, the formation of the deiodinated products **15** and **16** was accompanied by formation of the diynes **17b–d** which were isolated in 60–90% yields (Table 1). We further studied this side reaction and have made the following observations.

1. Under prolonged heating (6 h) of a benzene solution of 4-iodopyrazole **11** and $Pd(PPh_3)_4$ under an argon atmosphere, the reaction mixture (according to TLC) remained constant. The TLC of the reaction mixture showed the spot corresponding to the initial iodide **11** (R_f = 0.68, chloroform–acetone = 5 : 1 v/v).

2. The reaction of stoichiometric amounts of 5-iodopyrazole **3** with $Pd(PPh_3)_4$ in benzene at reflux resulted in the formation of the bis(triphenylphosphine)[4-(*N*-acetylamino)-1,3-dimethylpyrazol-5-yl]palladium(II) iodide **18** in 89% isolated yield. In



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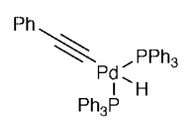


19

1 h, the TLC of the reaction mixture showed no spot corresponding to iodide **3**. There were two spots with R_f = 0.70 (benzene–hexane = 1 : 1 v/v) and R_f = 0.27 (chloroform–acetone = 5 : 1 v/v, iodine developed) corresponding to triphenylphosphine and complex **18** respectively.

3. The stoichiometric reaction of $Pd(PPh_3)_4$ with phenylacetylene **5b** in benzene at reflux gave, in 5 min, bis(triphenylphosphine)phenylethynylpalladium(II) hydride **19**[12] in 80% isolated yield. The TLC of the reaction mixture had the spot with R_f = 0.70 (benzene–hexane = 1 : 1 v/v), corresponding to triphenylphosphine. When an equivalent of 4-iodopyrazole **11** was added to the reaction mixture, in 30 min *N*-acetylaminopyrazole **15** was formed in 54% yield (R_f = 7.70, benzene–hexane = 1 : 1 v/v). The spot with R_f = 0.68 (chloroform–acetone = 5 : 1 v/v; iodide **11**) vanished.

4. The reaction of complex **19** with 5-iodopyrazole **3** gave complex **18** in a 13% yield. In this case, TLC shown a spot corresponding to triphenylphosphine. For this stoichiometric reaction, the alkynylhydride complex **19** and iodide **18** were in equilibrium which depended on the constants of the corresponding reactions of complex formation. It was likely that upon acetylene condensation and in the presence of the catalytic amount of palladium complex, only the hydride complex **19** was formed which, however, did not reduce the iodopyrazole **3**.

5. The presence of alkyne in the reaction was necessary for 4-iodopyrazole reduction. Thus, heating iodopyrazole **11** in Et_3N in the presence of the catalytic amounts of $Pd(PPh_3)_2Cl_2$ and CuI for 8 h, gave the initial iodopyrazole **11** in 69% yield. In this case, the deiodinated pyrazole **15** (according to TLC) was not formed.

Using these data and the relation to the mechanism of cross-coupling of alk-1-ynes with aromatic halides, we assumed that the mechanism of deiodination may be represented as an interaction of bis(triphenylphosphine)phenylethynylpalladium(II) hydride with the 4-iodopyrazole, giving rise to the complex bis(triphenylphosphine)phenylethynylpalladium(II) iodide[13] which, due to the reductive elimination of 1-iodoalkyne and subsequent addition of alk-1-yne, converts into the initial palladium complex (Fig. 1). Further, the interaction of 1-iodoalkynes with the initial alkyne in the presence of CuI and Et_3N (the Cadiot–Chodkiewicz reaction) results in formation of the observed disubstituted butadiynes **17**. This mechanism was confirmed by the fact that the cross-coupling of iodopyrazole **11** with alkyne **5b** in the presence of equimolar amounts of CuI and catalytic amounts of $Pd(PPh_3)_2Cl_2$ led to the formation of alkynylpyrazole **13b** in 72% isolated yield.

Taking into account the differences in the mechanisms of the Cu- and Pd-catalyzed coupling reactions, we hoped that the foregoing difficulties might again be overcome by resorting to the Stephens–Castro copper acetylide method[6] to access the alkynylpyrazoles **13** and **14**. Thus, iodides **11** and **12** were treated with copper acetylides in pyridine at 110–115 °C. Under these conditions, both iodopyrazoles were again relatively unreactive: couplings with copper acetylides **6b–d** required 14–18 h. However, generally good yields of the coupled products were secured; subsequent hydrolysis of the resulting (*N*-acetylamino)pyrazoles **13b–d** and **14b–d** in aqueous ethanolic sodium hydroxide at reflux gave the corresponding free amines **20b–d** and **21b–d**, also in good yields (Scheme 4).

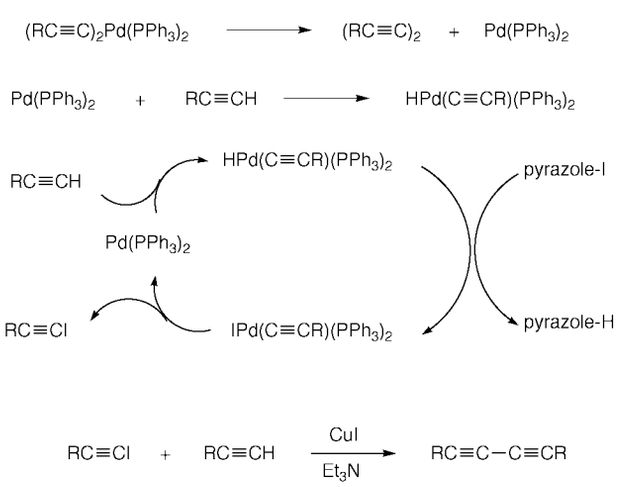
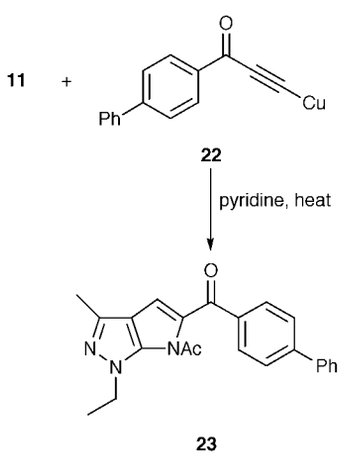


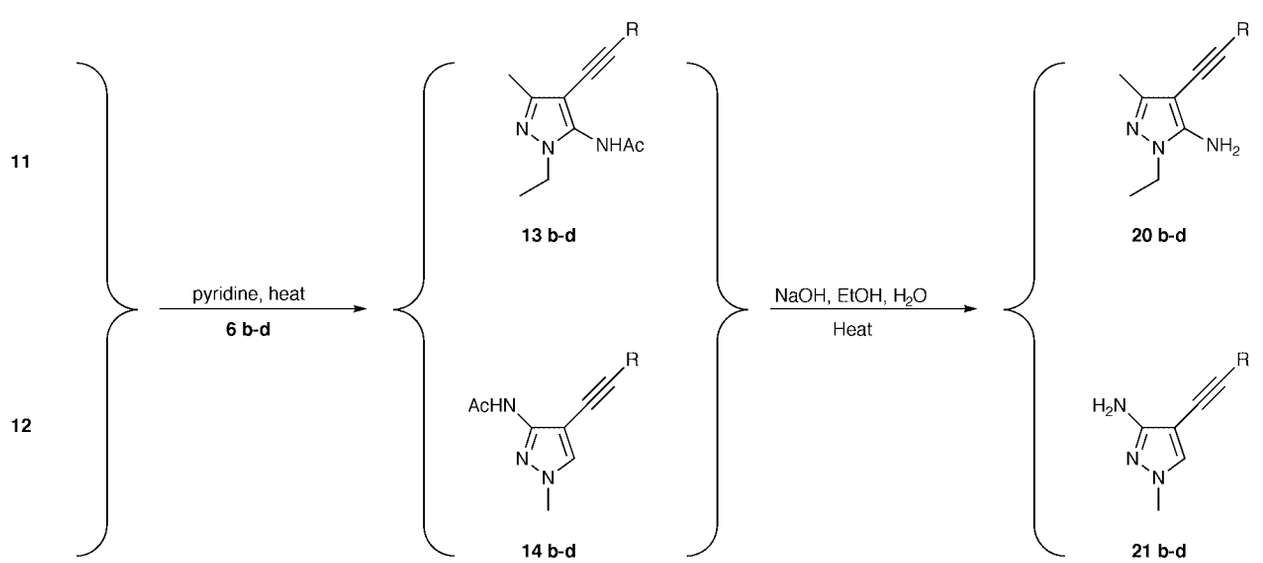
Fig. 1

Thus, cross-coupling of 4-iodopyrazoles **11** and **12** using the Pd(0) complex occurred only with relatively high CH-acidic acetylenes and the more vigorous copper acetylide method for halide substitution by an acetylene group is evidently more general. However, condensation of aryl halides with a functional group in the vicinal position can often be followed by cyclisation of the primary reaction products. The foregoing syntheses of *vic*-aminoalkynylpyrazoles were possible due to their low reactivity in such cyclisations, probably due to the strain inherent in a condensed system consisting of two 5-membered heterocycles. Thus, attempts to cyclize 5-(acetylamino)-1-ethyl-3-methyl-4-phenylethynylpyrazole **13b** in the presence of CuI or copper phenylacetylide in DMF at 150 °C failed.[3] However, cross-coupling of iodopyrazole **11** with copper *p*-phenylbenzoylacetylide **22** gave pyrrolo[2,3-*c*]pyrazole **23** directly [reaction (3)]; presumably, cyclisation is aided by the ketone group.



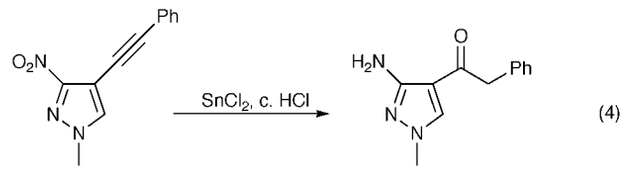
(3)

Unlike aminoiodopyrazoles and their *N*-acetyl derivatives, the cross-coupling of iodonitropyrazoles with alk-1-ynes proceeds quite easily and under mild conditions.[14] It was expected that this transformation, in combination with subsequent reduction of a nitro group, would be the experimentally simplest way of producing alkynylaminopyrazoles. However, this proved



Scheme 4

not to be the case. We decided to try and verify this assumption by reduction of 1-methyl-3-nitro-4-phenylethynylpyrazole **24** using tin(II) chloride in concentrated hydrochloric acid at 60–70 °C for 0.5 h. However, reduction was accompanied by hydration of the triple bond and resulted in formation of the aminoketone **25** [reaction (4)], the structure of which was con-



(4)

24 **25**

firmed by spectroscopic and analytical data, as well as by transformation into the known 1-methyl-4-phenylacetylpyrazole.[15] On the other hand, direct acid hydration of aminoalkynylpyrazole **21b** proceeded with great difficulty even under rather vigorous conditions (concentrated hydrochloric acid at reflux for 12 h) to give a poor yield of the aminoketone **25**. Other attempts to obtain the latter ketone **25** by reduction and hydration of aminoalkynylpyrazole **24** were unsuccessful.

Experimental

General details

All commercial reagents were used directly as obtained, unless otherwise noted. Copper(I) phenylacetylide **6b**, (4-methoxyphenyl)acetylide **6c**, octynide **6d** and *p*-phenylbenzoylacetylide **6e** were prepared according to the published procedure.[6] Amino- and (*N*-acetylamino)-iodopyrazoles **1**–**4**, **11** and **12** were prepared by previously reported methods[4] as was bis-(triphenylphosphine)phenylethynylpalladium(II) hydride **19**.[12] Pyridine and triethylamine were dried over sodium hydroxide pellets and distilled. Analytical TLC plates were "Silufol"® (SILPEARL on aluminum foil, UV 254, Czechoslovakia). Silica gel "KSK" (Russia, 100–200 mesh, air dried) was used for column chromatography. Melting points were determined with a Kofler apparatus and are uncorrected. IR spectra were obtained using chloroform solutions, unless otherwise stated, on a UR-20 spectrophotometer. ^{1}H NMR spectra were recorded at 90 MHz using a JEOL FX-90Q spectrometer at room temperature. Unless otherwise stated, all spectra were determined using dilute solutions in deuteriochloroform and tetramethylsilane as internal standard. Coupling constants are quoted in Hertz. Mass spectra were recorded on a Finnigan MAT-8200 instrument using electron impact ionization at 70 eV.

Pd–Cu couplings: general procedure

The iodopyrazole (10 mmol), the alk-1-yne (12 mmol), $Pd(PPh_3)_2Cl_2$ (80 mg) and copper(I) iodide (40 mg) were stirred together at 80 °C in triethylamine (30 ml) under an argon atmosphere for the time specified. The cooled reaction mixture was diluted with ether (300 ml) and filtered. The filtrate was concentrated and the residue chromatographed on silica gel.

Coupling with copper acetylides: general procedure

A mixture of the iodopyrazole (5.4 mmol) and the copper acetylide (6.0 mmol) in pyridine (40 ml) was refluxed under an argon stream for the time specified, then cooled and diluted with chloroform (50 ml). The resulting mixture was passed through a neutral alumina column (2 cm in length). The filtrate was evaporated and the residue taken up in chloroform. The resulting solution was washed in succession with 25% aqueous ammonia and water then dried over potassium carbonate and evaporated. The residue was purified by column chromatography on silica gel.

Hydrolysis of *N*-acetylaminopyrazoles: general procedure

The (*N*-acetylamino)pyrazole (10 mmol) in ethanol (20 ml) was treated with 25% aqueous sodium hydroxide (25 ml) and the mixture refluxed for 10–12 h, then cooled, diluted with water (100 ml) and extracted with chloroform (3 × 40 ml). The combined organic extracts were dried and evaporated and the residue chromatographed on silica gel.

4-Amino-1,3-dimethyl-5-(4-nitrophenyl)ethynylpyrazole 7a

Coupling between iodopyrazole **1** (1.40 g, 5.9 mmol) and alkyne **5a** (0.95 g, 6.5 mmol) for 0.5 h and purification on silica gel (ethyl acetate) gave the alkynylpyrazole **7a** (1.07 g, 71%) as a yellow crystalline solid, mp 215–216 °C (hexane–chloroform); ν_{max}/cm^{-1} 3480, 3400 (NH_2), 2230 (CC), 1540 (NO_2) and 1350; δ_H 2.20 (3H, s, 3-CH_3), 3.00 (2H, br s, NH_2), 3.75 (3H, s, N-CH_3), 7.70 (2H, d, *J* 8.9, 2′- and 6′-H) and 8.15 (2H, d, *J* 9.0, 3′- and 5′-H) [Found: C, 61.07; H, 4.62; N, 21.59. $C_{13}H_{12}N_4O_2$ requires C, 60.93; H, 4.72; N, 21.86%].

4-Amino-1,3-dimethyl-5-phenylethynylpyrazole 7b

(a) Reaction between the aminoiodopyrazole **1** (2.39 g, 10 mmol) and alk-1-yne **5b** (1.20 g, 12 mmol) for 6 h, work-up and chromatography on silica gel (chloroform) to give 1.83 g (86%) of the alkynylpyrazole **7b** as a light yellow solid, mp 62–64 °C (benzene–hexane) (lit.[4] mp 66–66.5 °C) which exhibited spectral and analytical data identical to those previously observed.[4]

(b) The (*N*-acetylamino)pyrazole **9b** (2.62 g, 10 mmol) in ethanol (20 ml) was hydrolysed with 25% aqueous sodium hydroxide (25 ml) in the usual manner. Chromatography on silica gel (5% ethyl acetate in chloroform) to give the alkynylpyrazole **7b** (1.87 g, 86%), mp 62–64 °C (benzene–hexane), identical with the foregoing sample.

4-Amino-1,5-dimethyl-3-(4-nitrophenyl)ethynylpyrazole 8a

Coupling between iodopyrazole **2** (0.89 g, 3.8 mmol) and alkyne **5a** (0.60 g, 4.1 mmol) for 1.5 h and purified on silica gel (10% ethyl acetate in chloroform) gave the *alkynylpyrazole* **8a** (0.71 g, 73%) as an orange crystalline solid, mp 216–217 °C (ethanol); ν_{max}/cm^{-1} 3480, 3400 (NH_2), 2230 (CC), 1540 (NO_2) and 1350; δ_H 2.21 (3H, s, 5-CH_3), 3.00 (2H, br s, NH_2), 3.80 (3H, s, N-CH_3), 7.65 (2H, d, *J* 9.0, 2′- and 6′-H) and 8.20 (2H, d, *J* 9.0, 3′- and 5′-H) [Found: C, 61.05; H, 4.68; N, 21.61%].

4-Amino-1,5-dimethyl-3-phenylethynylpyrazole 8b

(a) By the foregoing palladium-catalysed procedure, coupling of iodopyrazole **2** (2.0 g, 8.4 mmol) and alkyne **5b** (1.0 g, 9.8 mmol) for 8 h, and column chromatography on alumina (benzene) gave the *alkynylpyrazole* **8b** (0.64 g, 36%) as a white crystalline solid, mp 138.5–139.5 °C (carbon tetrachloride); ν_{max}/cm^{-1} 3425, 3360 (NH_2) and 2200 (CC) [Found: M^+, 211.1110. $C_{13}H_{13}N_3$ requires *M*, 211.1109] [Found: C, 73.82; H, 6.39; N, 19.65. $C_{13}H_{13}N_3$ requires C, 73.90; H, 6.20; N, 19.89%].

(b) Hydrolysis of alkynylpyrazole **10b** (3.86 g, 15 mmol) as described in the foregoing preparation of analogue **7b** and purification in the same manner gave the free *amine* **8b** (2.96 g, 92%), mp 138–139 °C (chloroform–hexane), identical with the foregoing sample.

4-Amino-1,3-dimethyl-5-(4-methoxyphenyl)ethynylpyrazole 7c

Hydrolysis of the *N*-acetylpyrazole **9c** (1.33 g, 4.7 mmol) as described in the general procedure but for 17 h gave the *amine* **7c** (0.98 g, 87%), mp 186–188 °C (hexane–chloroform); ν_{max}/cm^{-1} 3495, 3430 (NH_2) and 2225 (CC); δ_H 2.50 (3H, s, 3-CH_3), 2.30 (2H, br s, NH_2), 3.82 (3H, s, OCH_3), 3.95 (3H, s, N-CH_3), 6.75 (2H, d, *J* 8.6, 3′- and 5′-H) and 7.43 (2H, d, *J* 8.6, 2′- and 6′-H) [Found: C, 69.71; H, 5.64. $C_{14}H_{15}N_3O$ requires C, 69.69; H, 6.27%].

4-Amino-1,3-dimethyl-5-(octyn-1-y)pyrazole 7d

A solution of the *N*-acetyl-alkynylpyrazole **9d** (1.90 g, 7.3 mmol) in ethanol (70 ml) and 25% aqueous sodium hydroxide (15 ml) was refluxed for 12 h, then cooled and extracted with chloroform (3 × 40 ml). The combined extracts were passed through alumina (chloroform). The filtrate was concentrated and the residue was chromatographed on silica gel (elution with chloroform) to afford the *amine* **7d** (1.41 g, 88%) as a brown oil, ν_{max}/cm^{-1} 3495, 3400 (NH_2) and 2220 (CC); δ_H 0.85 (3H, t, *J* 8.2, $(CH_2)_5CH_3$), 1.20–1.50 (8H, m, $(CH_2)_4CH_3$), 2.20 (3H, s, 3-CH_3), 2.30 (2H, br s, NH_2), 2.45 (2H, t, *J* 7.3, CH_2CC) and 3.80 (3H, s, N-CH_3) [Found: N, 19.46. $C_{13}H_{21}N_3$ requires N, 19.16%].

4-Amino-1,5-dimethyl-3-(4-methoxyphenyl)ethynylpyrazole 8c

By the usual procedure, hydrolysis of the *N*-acetylpyrazole **10c** (2.66 g, 9.4 mmol) for 17 h and purification by column chromatography on silica gel (chloroform) gave the *amine* **8c** (1.81 g, 80%) as white needles, mp 148–149 °C (benzene); ν_{max}/cm^{-1} 3490, 3410 (NH_2) and 2225 (CC); δ_H 2.10 (3H, s, 5-CH_3), 2.50 (2H, br s, NH_2), 3.60 (3H, s, OCH_3), 3.85 (3H, s, N-CH_3), 6.80 (2H, d, *J* 8.4, 3′- and 5′-H) and 7.45 (2H, d, *J* 8.4, 2′- and 6′-H) [Found: C, 69.62; H, 5.90; N, 17.46. $C_{14}H_{15}N_3O$ requires C, 69.69; H, 6.27; N, 17.41%].

4-Amino-1,5-dimethyl-3-(octyn-1-yl)pyrazole 8d

By the usual procedure, hydrolysis of the *N*-acetylpyrazole **10d** (3.90 g, 4.9 mmol), followed by purification by column chromatography on alumina (benzene) gave the *amine* **8d** (2.82 g, 86%) as a yellow oil; ν_{max}/cm^{-1} 3505, 3415 (NH_2) and 2220 (CC); δ_H 0.85 (3H, t, *J* 8.0, $(CH_2)_5CH_3$), 1.15–1.45 (6H, m, $(CH_2)_3CH_3$), 1.50–1.60 (2H, m, CH_2CH_2CC), 2.25 (2H, br s, NH_2), 2.50 (3H, s, 5-CH_3), 2.40 (2H, t, *J* 7.0, CH_2CC) and 3.90 (3H, s, N-CH_3) [Found: M^+, 219.1736. $C_{13}H_{21}N_3$ requires *M*, 219.1735]. A microanalytical sample was not obtained.

4-(*N*-Acetylamino)-1,3-dimethyl-5-(4-nitrophenyl)ethynylpyrazole 9a

By the usual procedure, coupling between iodopyrazole **3** (1.0 g, 3.6 mmol) and alkyne **5a** (0.60 g, 4.1 mmol) in triethylamine (25 ml) was complete after 0.5 h. The cooled reaction mixture was diluted with chloroform (30 ml) and the resulting mixture passed through a neutral alumina column (4 cm in length) and the filtrate evaporated. The residue was washed in turn with hexane (20 ml), saturated aqueous sodium carbonate (25 ml), and water. The resulting solid residue was purified by column chromatography on silica gel (chloroform) to give the *alkynylpyrazole* **9a** (0.94 g, 88%) as yellow crystals, mp 227–228 °C (chloroform); ν_{max}/cm^{-1} 3400 (NH), 2230 (CC), 1720 (C=O), 1525 (NO_2) and 1345; δ_H 2.20 (6H, s, $COCH_3$ and 3-CH_3), 3.90 (3H, s, N-CH_3), 7.60 (2H, d, *J* 9.0, 2′- and 6′-H) and 8.22 (2H, d, *J* 9.0, 3′- and 5′-H) [Found: C, 60.42; H, 4.77; N, 18.60. $C_{15}H_{14}N_4O_3$ requires C, 60.40; H, 4.73; N, 18.78%].

4-(*N*-Acetylamino)-1,5-dimethyl-3-(4-nitrophenyl)ethynylpyrazole 10a

Cross-coupling of iodopyrazole **4** (0.50 g, 1.8 mmol) with alkyne **5a** (0.32 g, 2.2 mmol) as described in the general procedure, but for 1.5 h, afforded the *alkynylpyrazole* **10a** (0.39 g, 73%) as yellow crystals, mp 195–196 °C (chloroform); ν_{max}/cm^{-1} 3400 (NH), 2230 (CC), 1700 (C=O), 11540 (NO_2) and 1350; δ_H 2.25 (6H, s, $COCH_3$ and 5-CH_3), 3.90 (3H, s, N-CH_3), 6.85 (1H, br s, NH), 7.80 (2H, d, *J* 9.0, 2′- and 6′-H) and 8.30 (2H, d, *J* 9.0, 3′- and 5′-H) [Found: C, 60.78; H, 4.50; N, 18.61%].

4-(*N*-Acetylamino)-1,3-dimethyl-5-phenylethynylpyrazole 9b

Using the general method, coupling of iodopyrazole **3** (2.62 g, 9.4 mmol) and copper acetylide **6b** (1.65 g, 10 mmol) in refluxing pyridine (30 ml) for 6 h, followed by PTLC on silica gel (20 : 1 chloroform–acetone) gave the *alkynylpyrazole* **9b** (1.95 g, 82%) as a white crystalline solid, mp 186–187 °C (hexane–chloroform); ν_{max}/cm^{-1} 3410 (NH), 2220 (CC) and 1700 (C=O); δ_H 2.20 (3H, s, 3-CH_3), 2.25 (3H, s, $COCH_3$), 3.90 (3H, s, N-CH_3) and 7.55–7.65 (5H, m, Ph) [Found: M^+, 253.1216. $C_{15}H_{15}N_3O$ requires *M*, 253.1215] [Found: C, 70.93; H, 5.91; N, 16.53. $C_{15}H_{15}N_3O$ requires C, 71.13; H, 5.97; N, 16.59%].

4-(*N*-Acetylamino)-1,3-dimethyl-5-(4-methoxyphenyl)ethynylpyrazole 9c

By the general procedure, iodopyrazole **3** (0.70 g, 2.5 mmol) was coupled with copper acetylide **6c** (0.60 g, 3.1 mmol) in pyridine (20 ml). Complete consumption of starting material required 8 h. Purification of the crude product (neutral alumina, elution with chloroform) gave the *alkynlpyrazole* **9c** (0.40 g, 56%), mp 143–144 °C (benzene); δ_H 2.15 (6H, s, $COCH_3$ and 3-CH_3), 3.90 (3H, s, N-CH_3), 3.95 (3H, s, OMe), 6.85 (2H, d, *J* 8.6, 3′- and 5′-H) and 7.45 (2H, d, *J* 8.6, 2′- and 6′-H) [Found: M^+, 283.1320. $C_{16}H_{17}N_3O_2$ requires *M*, 283.1321] [Found: C, 67.65; H, 6.14; N, 14.75. $C_{16}H_{17}N_3O_2$ requires C, 67.83; H, 6.05; N, 14.83%].

4-(*N*-Acetylamino)-1,3-dimethyl-5-(octyn-1-yl)pyrazole 9d

Iodopyrazole **3** (1.50 g, 5.4 mmol) was coupled with copper acetylide **6d** (1.04 g, 6.0 mmol) by the general procedure for 10 h. Purification by column chromatography on silica gel (chloroform) followed by recrystallization from chloroform–hexane to afford the *alkynylpyrazole* **9d** (1.04 g, 74%) as a white powder, mp 156–157 °C; ν_{max}/cm^{-1} 3490 (NH), 2220 (CC) and 1710 (C=O); δ_H 0.85 [3H, t, *J* 8.2, $(CH_2)_5CH_3$], 1.20–1.50 [8H, m, $(CH_2)_4CH_3$], 2.15 (3H, s, 3-CH_3), 2.20 (3H, s, $COCH_3$), 2.40 (2H, t, *J* 7.3, CH_2CC) and 3.70 (3H, s, N-CH_3) [Found: M^+, 261.1842. $C_{15}H_{23}N_3O$ requires *M*, 261.1841] [Found: C, 68.96; H, 8.82; N, 15.96. $C_{15}H_{23}N_3O$ requires C, 68.93; H, 8.87; N, 16.08%].

4-(*N*-Acetylamino)-1,5-dimethyl-3-phenylethynylpyrazole 10b

A mixture of iodopyrazole **4** (4.0 g, 14 mmol) and copper acetylide **6b** (2.64 g, 16 mmol) was refluxed in pyridine (40 ml) for 4 h. After cooling, the reaction mixture was diluted with ether (100 ml), filtered and concentrated on a rotary evaporator. The resulting brown gum was chromatographed on silica gel (chloroform). Crystallization of the product from hexane–benzene gave the *alkynylpyrazole* **10b** (2.83 g, 78%) as white needles, mp 203–204 °C; ν_{max}/cm^{-1} 3430 (NH), 2230 (CC) and 1715 (C=O); δ_H 2.25 (3H, s, 5-CH_3), 2.30 (3H, s, $COCH_3$), 3.90 (3H, s, N-CH_3) and 7.60–7.70 (5H, m, Ph) [Found: M^+, 253.1214. $C_{15}H_{15}N_3O$ requires *M*, 253.1215] [Found: C, 71.28; H, 6.09; N, 16.48. $C_{15}H_{15}N_3O$ requires C, 71.13; H, 5.97; N, 16.59%].

4-(*N*-Acetylamino)-1,5-dimethyl-3-(4-methoxyphenyl)ethynylpyrazole 10c

By the usual method, coupling of iodopyrazole **4** (1.77 g, 6.3 mmol) with copper acetylide **6c** (1.42 g, 7.3 mmol) in refluxing pyridine (30 ml) for 6 h, followed by purification by column chromatography on alumina (benzene) gave the *alkynylpyrazole* **10c** (1.24 g, 69%) as a white crystalline solid, mp 168–169 °C (benzene); δ_H 2.20 (6H, s, $COCH_3$ and 5-CH_3), 3.85 (3H, s, N-CH_3), 3.89 (3H, s, OMe), 6.90 (2H, d, *J* 8.5, 3′- and 5′-H) and 7.45 (2H, d, *J* 8.5, 2′- and 6′-H) [Found: M^+, 283.1323. $C_{16}H_{17}N_3O_2$ requires *M*, 283.1321] [Found: C, 67.65; H, 6.04; N, 15.05. $C_{16}H_{17}N_3O_2$ requires C, 67.83; H, 6.05; N, 14.83%].

4-(*N*-Acetylamino)-1,5-dimethyl-3-(octyn-1-yl)pyrazole 10d

By the usual method, coupling of iodopyrazole **4** (1.90 g, 6.8 mmol) and copper acetylide **6d** (1.35 g, 7.8 mmol) in refluxing

pyridine (30 ml) for 8 h and purification by PTLC on alumina (benzene) gave the *alkynylpyrazole* **10d** (1.20 g, 73%), mp 157.5–158 °C (hexane–chloroform); ν_{max}/cm^{-1} 3425 (NH), 2215 (CC) and 1710 (C=O); δ_H 0.85 [3H, t, *J* 8.2, $(CH_2)_5CH_3$], 1.20–1.40 [6H, m, $(CH_2)_3CH_3$], 1.48–1.60 (2H, m, CH_2CH_2CC), 2.18 (3H, s, 5-CH_3), 2.22 (3H, s, $COCH_3$), 2.40 (2H, t, *J* 7.3, CH_2CC) and 3.80 (3H, s, N-CH_3) [Found: M^+, 261.1843. $C_{15}H_{23}N_3O$ requires *M*, 261.1841] [Found: C, 69.03; H, 8.71; N, 6.17. $C_{15}H_{23}N_3O$ requires C, 68.93; H, 8.87; N, 16.08%].

5-(*N*-Acetylamino)-1-ethyl-3-methyl-4-(4-nitrophenyl)ethynylpyrazole 13a

By the general procedure, coupling of iodopyrazole **11** (0.73 g, 2.5 mmol) with alk-1-yne **5a** (0.45 g, 3.1 mmol) for 5.5 h gave, after purification by silica gel chromatography (elution with 5% ethyl acetate in chloroform), the *alkynylpyrazole* **13a** (0.49 g, 63%) as yellow crystals, mp 188–189 °C (benzene–chloroform); ν_{max}/cm^{-1} 3390 (NH), 2230 (CC), 1715 (C=O), 1530 (NO_2) and 1350; δ_H 1.68 (3H, t, *J* 7.2, CH_2CH_3), 2.33 (3H, s, 3-CH_3), 2.38 (3H, s, $COCH_3$), 4.00 (2H, q, *J* 7.2 N-CH_2), 7.65 (2H, d, *J* 8.8, 2′- and 6′-H) and 8.10 (2H, d, *J* 8.8, 3′- and 5′-H) [Found: C, 61.63; H, 5.18; N, 17.72. $C_{16}H_{16}N_4O_3$ requires C, 61.53; H, 5.16; N, 17.94%].

3-(*N*-Acetylamino)-1-methyl-4-(4-nitrophenyl)ethynylpyrazole 14a

Coupling of iodopyrazole **12** (0.90 g, 3.4 mmol) and alk-1-yne **5a** (0.60 g, 4.15 mmol) for 6 h, followed by column chromatography on silica gel (elution with chloroform) gave the *alkynylpyrazole* **14a** (0.56 g, 58%) as yellow crystals, mp 241–241.5 °C (chloroform–ethanol); ν_{max}/cm^{-1} 3400 (NH), 2230 (CC), 1710 (C=O), 1530 (NO_2) and 1350; δ_H 2.25 (3H, s, $COCH_3$), 3.90 (3H, s, N-CH_3), 7.50 (2H, d, *J* 9.0, 2′- and 6′-H), 7.72 (1H, s, 5-H) and 8.22 (2H, d, *J* 9.0, 3′- and 5′-H) [Found: C, 59.04; H, 4.18; N, 19.46. $C_{14}H_{12}N_4O_3$ requires C, 59.15; H, 4.25; N, 19.71%].

5-(*N*-Acetylamino)-1-ethyl-3-methyl-4-phenylethynylpyrazole 13b

Iodopyrazole **11** (2.93 g, 0.01 mol) and copper acetylide **6b** (1.80 g, 0.11 mole) were refluxed together in pyridine (30 ml) for 16 h. Purification by column chromatography on alumina (benzene) gave the *alkynylpyrazole* **13b** (2.09 g, 78%) as a white crystalline solid, mp 161–162 °C (chloroform–hexane); ν_{max}/cm^{-1} 3420 (NH), 2225 (CC) and 1700 (C=O); δ_H 1.65 (3H, t, *J* 7.1, CH_2CH_3), 2.15 (3H, s, 3-CH_3), 2.30 (3H, s, $COCH_3$), 4.10 (2H, q, *J* 7.1, CH_2N) and 7.60–7.70 (5H, m, Ph) [Found: C, 71.44; H, 6.20. $C_{16}H_{17}N_3O$ requires C, 71.88; H, 6.41%].

5-(*N*-Acetylamino)-1-ethyl-3-methyl-4-(4-methoxyphenyl)-ethynylpyrazole 13c

Following the general procedure, iodopyrazole **11** (1.0 g, 3.4 mmol) and copper acetylide **6c** (0.70 g, 3.6 mmol) in pyridine (30 ml) were heated together for 14 h. After the usual workup, chromatography (silica gel, chloroform) provided the *alkynylpyrazole* **13c** (0.48 g, 47%) as a white solid, mp 133–134 °C (hexane–benzene); δ_H 1.63 (3H, t, *J* 7.1, CH_2CH_3), 2.00 (3H, s, 3-CH_3), 2.10 (3H, s, $COCH_3$), 3.80 (3H, s, OCH_3), 4.00 (2H, q, *J* 7.1, CH_2N), 6.85 (2H, d, *J* 9.0, 3′- and 5′-H) and 7.40 (2H, d, *J* 9.0, 2′- and 6′-H); *m*/*z* 297 (M^+, 100%).

5-(*N*-Acetylamino)-1-ethyl-3-methyl-4-(octyn-1-yl)pyrazole 13d

Iodopyrazole **11** (1.0 g, 3.4 mmol) and copper acetylide **6d** (0.65 g, 3.8 mmol) were heated in refluxing pyridine (40 ml) for 18 h. After cooling, the reaction mixture was diluted with ether (100 ml) and passed through a neutral alumina column (3 cm in length). The filtrate was concentrated on a rotary evaporator to yield a brown oil that was twice chromatographed on silica gel (benzene) to give a yellow gum which solidified on storage. Recrystallization from benzene gave the *alkynylpyrazole* **13d** (0.76 g, 81%) as a white powder, mp 113–114 °C; ν_{max}/cm^{-1} 3415 (NH), 2215 (CC) and 1710 (C=O); δ_H 0.80 [3H, br t, *J* 8.2, $(CH_2)_5CH_3$], 1.20–1.50 [8H, m, $(CH_2)_4CH_3$], 1.68 (3H, t, *J* 7.0, CH_3CH_2), 2.11 (3H, s, 3-CH_3), 2.20 (3H, s, $COCH_3$), 2.50 (2H, t, *J* 7.6, CH_2CC) and 3.95 (2H, q, *J* 7.0, CH_2N) [Found: M^+, 275.1995. $C_{16}H_{25}N_3O$ requires *M*, 275.1998] [Found: C, 69.77; H, 9.07; N, 15.27. $C_{16}H_{25}N_3O$ requires C, 69.78; H, 9.15; N, 15.26%].

3-(*N*-Acetylamino)-1-methyl-4-phenylethynylpyrazole 14b

Coupling between iodopyrazole **12** (2.62 g, 0.01 mol) and copper acetylide **6b** (1.75 g, 0.011 mol) in refluxing pyridine (40 ml) for 12 h, followed by the usual work-up gave reasonably pure alkynylpyrazole **14b** (1.7 g, 72%) which was converted into amine **16b** without further purification.

3-(*N*-Acetylamino)-1-methyl-4-(4-methoxyphenyl)ethynylpyrazole 14c

Reaction of iodopyrazole **12** (2.62 g, 0.01 mol) and copper acetylide **6c** (3.0 g, 0.015 mol) in refluxing pyridine (30 ml) for 14 h followed by the usual work-up and column chromatography on silica gel (chloroform) gave a white, waxy solid (1.71 g, 64%). An analytical sample was obtained by recrystallization (chloroform–hexane) to afford the *alkynylpyrazole* **14c** as white crystals, mp 131–132 °C; ν_{max}/cm^{-1} 3400 (NH), 2230 (CC) and 1700 (C=O); δ_H 2.70 (3H, s, $COCH_3$), 3.85 (3H, s, N-CH_3), 4.05 (3H, s, OCH_3), 6.15 (1H, br s, NH), 6.88 (2H, d, *J* 8.5, 3′- and 5′-H), 7.36 (2H, d, *J* 8.5, 2′- and 6′-H) and 7.37 (1H, s, 5-H) [Found: C, 66.67; H, 5.57; N, 15.71. $C_{15}H_{15}N_3O_2$ requires C, 66.90; H, 5.61; N, 15.60%].

[4-(*N*-Acetylamino)-1,3-dimethylpyrazol-5-yl]bis(triphenylphosphine)palladium(II) iodide 18

(a) A mixture of 5-iodopyrazole **3** (0.07 g, 0.25 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.30 g, 0.26 mmol) in benzene (20 ml) was heated under argon at 80 °C for 5 min. After cooling, the reaction mixture was diluted with pentane (50 ml). The resulting solid was filtered off, washed with pentane and chromatographed on silica gel (chloroform) to afford orange crystals of the *palladium iodide* **18** (0.21 g, 89%), mp 190 °C (decomp.); δ_H 2.05 (3H, s, 3-CH_3), 2.25 (3H, s, $COCH_3$), 3.60 (3H, s, N-CH_3) and 7.25–7.65 (30H, m, 6 × Ph) [Found: C, 56.97; H, 4.50; I, 14.08. $C_{43}H_{40}IN_3OP_2Pd$ requires C, 56.75; H, 4.43; I, 13.95%].

(b) A mixture of bis(triphenylphosphine)phenylethynylpalladium(II) hydride **19**[12] (0.73 g, 1.0 mmol) and iodopyrazole **3** (0.28 g, 1.0 mmol) in benzene (20 ml) was heated under argon at 80 °C for 0.5 h. After cooling, the reaction mixture was concentrated and diluted with pentane (50 ml). The resulting solid was filtered off, washed with pentane and chromatographed on silica gel (chloroform) to afford iodide **18** (0.12 g, 13%), which exhibited spectroscopic and analytical data identical with the foregoing sample.

5-Amino-1-ethyl-3-methyl-4-phenylethynylpyrazole 20b

By the usual procedure, hydrolysis of the *N*-acetylpyrazole **13b** (2.67 g, 10 mmol) for 13 h and column chromatography on silica gel (chloroform) gave *amine* **20b** (1.55 g, 69%) as yellow needles, mp 119–120 °C (hexane–benzene); ν_{max}/cm^{-1} 3460, 3380 (NH_2) and 2215 (CC); δ_H 1.40 (3H, t, *J* 7.5. CH_3CH_2), 1.65 (2H, br s, NH_2), 2.30 (3H, s, 3-CH_3), 3.90 (2H, q, *J* 7.5, N-CH_2) and 7.20–7.50 (5H, m, Ph) [Found: C, 74.61; H, 6.72; N, 18.62. $C_{14}H_{15}N_3$ requires C, 74.64; H, 6.71; N, 18.65%].

5-Amino-1-ethyl-3-methyl-4-(octyn-1-yl)pyrazole 20d

By the usual procedure, hydrolysis of the *N*-acetylpyrazole **13d** (2.75 g, 10 mmol) for 30 h followed by column chromatography

on alumina (benzene) to give the *amine* **20d** (1.71 g, 73%) as a brown oil; ν_{max}/cm^{-1} 3500, 3415 (NH_2) and 2200 (CC); δ_H 0.90 [3H, t, *J* 8.1, $(CH_2)_5CH_3$], 1.20–1.60 [11H, m, $(CH_2)_4CH_3$ and CH_3CH_2-N], 2.20 (3H, t, *J* 7.2, CH_2CC), 2.30 (2H, br s, NH_2), 2.45 (3H, s, 3-CH_3) and 3.90 (2H, q, *J* 7.5, N-CH_2) [Found: M^+, 233.1892. $C_{14}H_{23}N_3$ requires *M*, 233.1892]. A microanalytical sample was not obtained.

3-Amino-1-methyl-4-phenylethynylpyrazole 21b

By the usual procedure, hydrolysis of the *N*-acetylpyrazole **14b** (2.39 g, 10 mmol) for 14 h and column chromatography on silica gel (chloroform) gave the *amino* **21b** as white needles (1.59 g, 81%), mp 144–145 °C (carbon tetrachloride); ν_{max}/cm^{-1} 3482, 3400 (NH_2) and 2225 (CC); δ_H [$(CD_3)_2CO$] 2.08 (2H, br s, NH_2), 3.67 (3H, s, N-CH_3), 7.20–7.50 (5H, m, Ph) and 7.73 (1H, s, 5-H) [Found: C, 73.33; H, 5.65; N, 20.92. $C_{12}H_{11}N_3$ requires C, 73.07; H, 5.62; N, 21.30%].

6-Acetyl-1-ethyl-3-methyl-5-(*p*-phenylbenzoyl)pyrrolo[3,4-*b*]-pyrazole 23

A mixture of iodopyrazole **11** (1.34 g, 4.6 mmol) and the benzoylacetylide **22** (1.23 g, 4.6 mmol) in pyridine (15 ml) was refluxed for 3 h then the solvent evaporated under vacuum. The brown viscous residue was treated with diethyl ether (5 ml). The crystals which separated were isolated and washed with ether. The crude product was dissolved in chloroform (5 ml) and purified by column chromatography on silica gel (elution with chloroform). Recrystallization from chloroform–benzene gave yellow needles of the *pyrrolopyrazole* **23** (0.95 g, 56%), mp 194–195 °C; ν_{max}/cm^{-1} 1630 (C=O); δ_H 1.50 (3H, t, *J* 7.2, 3 H, CH_2CH_3), 2.60 (3H, s, 3-CH_3), 2.65 (3H, s, $COCH_3$), 4.30 (2H, q, *J* 7.2, N-CH_2), 6.35 (1H, br s, NH), 7.30–7.55 (4H, m, 3′-, 5′-, 7′- and 9′-H), 7.65–7.75 (3H, m, 4′-, 6′- and 8′-H) and 8.00 (2H, d, *J* 8.5, 2′- and 10′-H); *m*/*z* 371 (M^+, 26%), 370 ($M^+ - H$, 100), 3.42 ($M^+ - C_2H_5$, 26), 327 ($M^+ - COCH_3$, 45), 217 (29) and 189 (48) [Found: $M^+ - H$, 370.1554. $C_{23}H_{20}N_3O_2$ requires *M*, 370.1555] [Found: C, 74.67; H, 5.86; N, 11.28. $C_{23}H_{21}N_3O_2$ requires C, 74.36; H, 5.70; N, 11.32%].

1-Methyl-3-nitro-4-phenylethynylpyrazole 24

4-Iodo-1-methyl-3-nitropyrazole[16] (2.53 g, 10 mmol), phenylacetylene **5b** (1.1 g, 11 mmol), $Pd(PPh_3)_2Cl_2$ (80 mg) and copper(I) iodide (40 mg) were stirred together at 50–60 °C in triethylamine (30 ml) under an argon atmosphere for 1 h. The cooled reaction mixture was diluted with ether (300 ml) and filtered. The filtrate was evaporated and the residue chromatographed on silica gel (benzene) to give the *nitropyrazole* **24** (2.18 g, 96%) as yellow needles, mp 115–116 °C (benzene); ν_{max}/cm^{-1} 2240 (CC), 1540 (NO_2) and 1350; δ_H 4.00 (3H, s, N-CH_3), 7.35–7.55 (5H, m, Ph) and 7.75 (1H, s, 5-H) [Found: C, 63.71; H, 4.08; N, 18.21. $C_{12}H_9N_3O_2$ requires C, 63.49; H, 3.99; N, 18.49%].

3-Amino-1-methyl-4-phenylacetylpyrazole 25

To a stirred suspension of the nitropyrazole **24** (0.6 g, 2.6 mmol) in concentrated hydrochloric acid (10 ml) at 60–70 °C was added dropwise a solution of tin(II) chloride (2.3 g, 10.2 mmol) in concentrated hydrochloric acid (20 ml). After 1 h, the hydrochloric acid was evaporated. The residue was quenched with water (50 ml), the mixture was neutralised with 40% aqueous sodium hydroxide and extracted with chloroform (3 × 30 ml). The combined extracts were dried and evaporated and the crude produce dissolved in ether, then precipitated by the addition of hexane. The precipitate was filtered off and crystallized from benzene–hexane to give the *aminopyrazole* **25** (0.51 g, 90%), mp 147–148 °C; ν_{max}/cm^{-1} 3500, 3400 (NH_2) and 1650 (C=O); δ_H 3.65 (2H, s, CH_2Ph), 3.90 (3H, s, N-CH_3), 5.20 (2H, br s, NH_2), 7.45 (1H, s, 5-H) and 7.10–7.25 (5H, m, Ph) [Found: C, 66.80; H, 6.04; N, 19.36. $C_{12}H_{13}N_3O$ requires C, 66.96; H, 6.09; N, 19.52%].

Reaction of bis(triphenylphosphine)phenylethynylpalladium(II) hydride 19 with 5-(*N*-acetylamino)-1-ethyl-4-iodo-3-methylpyrazole 11

A mixture of bis(triphenylphosphine)phenylethynylpalladium(II) hydride **19** (0.73 g, 1.0 mmol) and iodopyrazole **11** (0.29 g, 1.0 mmol) in benzene (20 ml) was heated under argon at 80 °C for 0.5 h. After cooling, the reaction mixture was concentrated and diluted with pentane (50 ml). The resulting solid was filtered off, washed with pentane and chromatographed on silica gel (chloroform) to give the *deiodinated pyrazole* **15** (0.09 g, 54%), mp 111–112 °C (benzene–hexane); ν_{max}/cm^{-1} 3420 (NH) and 1700 (C=O); δ_H 1.65 (3H, t, *J* 7.0, CH_2CH_3), 2.10 (3H, s, 3-CH_3), 2.25 (3H, s, $COCH_3$), 4.05 (2H, q, *J* 7.0, N-CH_2) and 6.30 (1H, s, 4-H) [Found: C, 57.44; H, 7.70. $C_8H_{13}N_3O$ requires C, 57.46; H, 7.84%].

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