Synthesis of 4-Alkylpyrazoles from 3,5-Diaminopyrazoles

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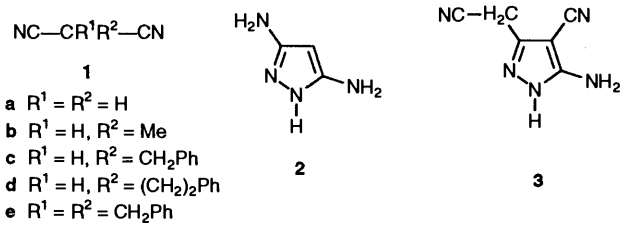
The possibility of preparing 4-alkylpyrazoles from malononitrile (through *C*-alkyl malononitriles and 3,5-diamino-4-alkylpyrazoles) has been explored. Although some difficulties arise in the double-deamination step, the method has allowed the synthesis of 4-benzyl- and 4-phenethyl-pyrazoles. New 3-halogenopyrazoles have also been prepared. The synthesis of 3,5-diamino-4-iodopyrazole is reported. This elusive compound has a ^{13}C NMR spectrum in which an aromatic carbon (C-4) appears at δ 29.53.

According to the literature,[1] malononitrile **1a** reacts with hydrazine to give a dark brown oily product the structure of which was assigned as **2**, although the only support for this was a nitrogen determination on a crystalline benzal derivative. Taylor and Hartke[2] also investigated this reaction and assigned structure **3** to the product. To explain the formation of **3** they proposed an initial dimerization of malononitrile followed by reaction with hydrazine. A summary of the situation until 1970 is given in reference 3.



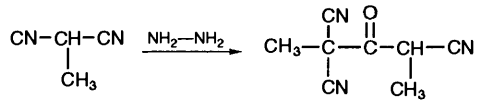
In the case of 3-amino-4-arylpyrazoles, it was reported that the amino group can be replaced by a hydrogen through the intermediate diazonium salt.[4] This led us to explore the possibility of preparing 4-alkylpyrazoles from their amino precursors, an interesting possibility, considering the difficulty of their syntheses.[5a]

We were interested in preparing new 4-alkylpyrazoles which could be inhibitors and de-activators of liver alcohol dehydrogenase,[5b] since one of them, 4-methylpyrazole, has been developed into a drug for the treatment of alcoholism. Two general methods have been described to prepare these pyrazoles, both being laborious. The first one is Reichardt's method[6] which uses *C*-monosubstituted malonaldehydes, which, in turn, are difficult to prepare.[7] Tolf's method[8] uses 4-alkylpyrazolin-5-ones and 4-alkyl-5-chloropyrazoles as intermediates but it is also lengthy and complicated to work-up.

Results and Discussion

Considering the results above summarized, we decided to attempt a new approach based on application of methodology recently presented, namely: (i) the easy preparation of *C*-alkylmalononitriles[9,10] and (ii) their reaction with hydrazine to afford 3,5-diamino-4-alkylpyrazoles (only described for 4-benzyl derivatives).[11] If these last compounds could be double-deaminated, then, a general procedure to prepare 4-alkylpyrazoles could be devised. The deamination of 3(5)-aminopyrazoles has been reported;[12,13] however, most of the cases studied involved derivatives bearing a substituent on the pyrazole nitrogen atom[13] or consecutive coupling reactions. The double deamination reaction of diaminopyrazoles was never reported nor the generalisation of the synthesis of 4-alkyl-3,5-diaminopyrazoles from alkylmalononitriles to substituents other than benzyl.

In our first attempt we allowed methylmalononitrile **1b** to react with hydrazine hydrate to give a red oil which, after column chromatography on silica gel, yielded 23% of a compound which was identified as compound **4**.



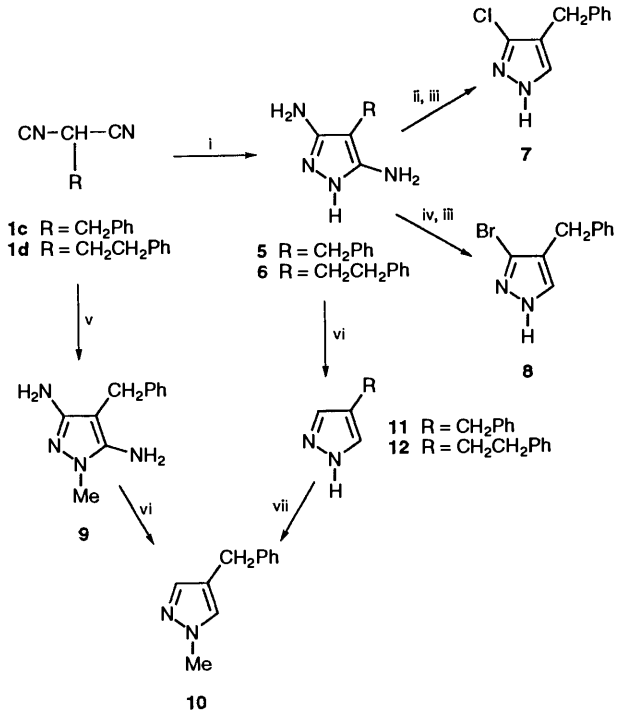
1b **4**

The expected 3,5-diamino-4-methylpyrazole was not formed (several attempts yielded only mixtures of **4** with other open-chain derivatives). Compound **4** is similar to the supposed precursor of **3**.

A repeat of the reaction of benzylmalononitrile **1c** gave the 3,5-diamino-4-benzylpyrazole **5**. The formation of compounds **5**, **7**, **8** and **11** (Scheme 1) has been described and the origin of the 3-halogeno derivatives discussed.[11,14,15]

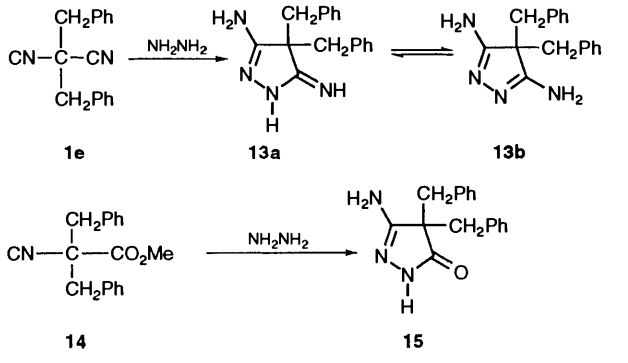
Since, to obtain pure 4-benzylpyrazole **11**, non-nucleophilic anion acids must be used, the simplest solution is to carry out the deamination in the presence of nitrous acid as the only acid, this being possible using sodium nitrite and aqueous phosphorous acid [$(HO)_2HP$]. 3,5-Diamino-4-benzyl-*N*-methylpyrazole **9** was prepared from **1c** and methylhydrazine, showing that substituted hydrazines also react with *C*-substituted malononitriles to afford pyrazoles. Compound **9** was deaminated under similar conditions to afford the corresponding 4-benzyl-1-methylpyrazole **10**. This last compound was also obtained by methylation of **11** with methyl iodide (identical picrates). Since the reactions of malononitrile **1a** and methylmalononitrile **1b** with hydrazine do not afford 3,5-diaminopyrazoles while that with benzylmalononitrile **1c** proceeds normally, we decided to use a phenethyl derivative as an intermediate case. The reaction worked normally and 3,5-diamino-4-phenethylpyrazole **6** was obtained using the same conditions (Scheme 1), but the necessary reaction time was 12 h instead of 8 h for the benzyl derivative. The deamination afforded the 4-phenethylpyrazole **12** in 45% yield.

Considering the previous results obtained when monoalkylmalononitriles react with hyrazine hydrate, we decided to explore the reactivity of dibenzylmalononitrile **1e**. It is known,



Scheme 1 *Reagents and conditions:* i, NH_2NH_2; ii, $NaNO_2$/HCl; iii, H_3PO_2; iv, $NaNO_2$/HBr; v, $MeNHNH_2$; vi, $NaNO_2$, H_3PO_2; vii, MeI, NaOH/DMF

that *C,C*-disubstituted β-keto esters and *C,C*-disubstituted β-cyanoacetates afford 4,4-disubstituted pyrazolidine-3,5-diones and 3-amino-4,4-disubstituted pyrazolin-5-ones.[3,5] The reaction was performed by heating the mixture of **1e** and hydrazine hydrate and afforded, by precipitation, a compound which was identified as 3,5-diamino-4,4-dibenzylisopyrazole **13** in 30% yield. This compound exists as a mixture of two tautomers, the imino, **13a**, and the amino, **13b**. We have verified that compound **13** is not the aminopyrazolinone **15**, preparing this last compound unequivocally from the β-keto ester **14** (Scheme 2).



Scheme 2

The structure of the compounds was established by using ^{13}C NMR spectroscopy and comparison with data from known pyrazoles;[16] this spectroscopy is very useful due to the sensitivity of ^{13}C chemical shifts to substituents like halogens and, especially, to the amino group (Table 1). From the examination of a large set of pyrazoles,[16] it has been established that these groups produce very large *ipso* and *ortho* effects in pyrazoles: bromo (*ipso* = −12.5 ppm), iodo (*ipso* = −45.3 ppm), amino (*ortho* = −12.3 to −16.5 ppm). It was expected that a combination of these SCS (substituent chemical shifts) lead to a very shielded carbon C-4 for 3,5-diamino-4-bromopyrazole **17**; that is what was observed, δ(C-4) = 62.86 ppm. To obtain a larger effect, an iodine atom at position 4 was necessary. However, 3,5-diamino-4-iodopyrazole **18** proved difficult to prepare. Conventional methods (see Experimental section) failed and only the new reagent, $[Ipy_2][BF_4]$[17] allowed us to obtain the desired compound. The compound presents a C-4 signal at 29.53 ppm which constitutes the most shielded C-4 carbon ever observed,[16] and probably one of the highest field aromatic carbons ever reported.

The other assignments were straightforward. Both methylenes in the 4-phenethyl derivatives **6** and **12** were assigned taking into account that the signal of the methyl group in 4-methylpyrazole (8.7 ppm) is much more shielded than in toluene (21.3 ppm).

Experimental

M.p.s were determined on a Reichert–Jung microscope apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were obtained for $CDCl_3$ or $[^2H_6]$-DMSO solutions on a Varian-Gemini 200 MHz spectometer. Mass measurements at low resolution were obtained on a Finnigan TSQ-70 spectrometer operating at 75 eV. Microanalyses were obtained at the Instituto de Quimica Organica General, CSIC, Madrid. Reagents and solvents were purchased from common commercial suppliers and were used without further purification. Yields were not optimized. Methylmalononitrile **1b**, benzylmalononitrile **1c** and dibenzylmalononitrile **1e**, were prepared according to methods previously described in the literature.[9,10]

Phenethylmalononitrile **1d**: *General Procedure.*—Malononitrile (25 mmol), phenethyl bromide (12.5 mmol) and tetrabutylammonium bromide (TBAB, 1.0 mmol) were stirred in a two-necked flask provided with a reflux condenser for 30 min at room temperature. Potassium *tert*-butoxide (12.5 mmol) was then added at 0 °C to the mixture and stirring was continued for 5 h. The crude mixture was extracted with dichloromethane (200 cm^3). Concentration of the extract and column chromatography on silica gel (Merck, 70–230 mesh) using toluene with eluent of the residue, afforded the pure compound (Found: C, 77.7; H, 6.1; N, 16.2. $C_{11}H_{10}N_2$ requires C, 77.62; H, 5.92; N, 16.46%); $\delta_H(CDCl_3)$ 7.36–7.19 (5 H, m, H_{arom}), 3.57 (1 H, t, CH), 2.95 (2 H, t, CH_2) and 2.36 (2 H, t, CH_2); $\delta_C(CDCl_3)$ 128.94, 128.90, 127.12 (C_{arom}), 112.41 (CN), 32.07, 30.1 (CH_2) and 21.44 (CH).

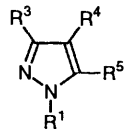
Synthesis of 3,5-Diamino-4-alkylpyrazoles: General Procedure.—The compounds were prepared following a procedure described in ref. 14. 3,5-*Diamino-4-benzylpyrazole* **5**. Recrystallized from ethyl acetate; yield 40%; m.p. 143–144 °C (lit.,[14] m.p. 150–151 °C) (Found: C, 63.6; H, 6.2; N, 30.0. $C_{10}H_{12}N_4$ requires C, 63.80; H, 6.43; N, 29.77%); *m/z* 188 (M^+); $\delta_H(CDCl_3)$ 7.43 (1 H, br, NH), 7.14 (5 H, s, H_{arom}), 3.98 (4 H, br, NH_2) and 3.51 (2 H, s, CH_2).

3,5-*Diamino-4-benzyl-1-methylpyrazole* **9**. Isolated by column chromatography on silica gel MN-60 (230–400 mesh from Machery-Nagel, Germany) using dichloromethane–methanol (9:1) as eluent; yield, after column chromatography, 12%; m.p. 103–105 °C (Found: C, 65.3; H, 6.9; N, 27.8. $C_{11}H_{14}N_4$ requires C, 65.31; H, 6.99; N, 27.70%); *m/z* 202 (M^+); $\delta_H(CDCl_3)$ 7.25 (5 H, m, H_{arom}), 3.59 (2 H, s, CH_2), 3.48 (3 H, s, CH_3) and 3.21 (4 H, br, NH_2).

3,5-*Diamino-4-phenethylpyrazole* **6**. Crystallized from ethyl acetate; yield 89%; m.p. 119–121 °C (Found: C, 65.0; H, 6.8; N, 28.2. $C_{11}H_{14}N_4$ requires C, 65.31; H, 6.99; N, 27.70%); *m/z* 202 (M^+); $\delta_H(CDCl_3)$, 7.19 (5 H, m, H_{arom}), 3.82 (5 H, br, NH), 2.75 (2 H, t, CH_2) and 2.52 (2 H, t, CH_2).

3,5-*Diamino-4,4-dibenzylisopyrazole* **13**. This compound was prepared following the same procedure of ref. 14 but starting

Table 1 ^{13}C chemical shifts of pyrazoles



Comp.	R^1	R^3	R^4	R^5	C-3	C-4	C-5	Substituents[a]	
5[a]	H	NH_2	CH_2Ph	NH_2	149.19	89.91	149.19	27.17 (CH_2)	141.15, 125.28, 127.85, 127.85
6[a]	H	NH_2	CH_2CH_2Ph	NH_2	149.05	89.14	149.05	23.92 (CH_2) 35.84 (CH_2)	141.80, 128.54*, 128.24*, 125.84
7[a]	H	Br	CH_2Ph	H	121.13	120.13	129.42	29.75 (CH_2)	138.57, 128.42, 128.36, 128.36
8[b]	H	H	CH_2Ph	H	132.98	119.83	132.98	30.38 (CH_2)	141.11, 126.02, 128.41, 128.41
9[a]	Me	NH_2	CH_2Ph	NH_2	142.63	89.61	151.24	28.19 (CH_2) 33.52 (NMe)	139.79, 128.52, 128.00, 126.14
10[a]	Me	H	CH_2Ph	H	138.82	120.69	128.65	30.44 (CH_2) 38.57 (NMe)	141.08, 128.31*, 128.60*, 125.90
11[a]	H	Cl	CH_2Ph	H	138.90	117.41	129.33	29.41 (CH_2)	139.77, 128.45, 128.45, 126.31
12[a]	H	H	CH_2CH_2Ph	H	132.82	120.38	132.82	25.93 (CH_2) 37.24 (CH_2)	141.60, 128.32, 128.32, 125.96
16[b]	H	NH_2	H	NH_2	151.83	76.24	151.83		—
17[b]	H	NH_2	Br	NH_2	148.52	62.82	148.52		—
18[b]	H	NH_2	I	NH_2	156.76	29.53	156.76		—

[a] Aromatic carbons are given in the order *ipso*, *ortho* (2C), *meta* (2C), *para*; * unassigned signals. [b] $CDCl_3$, [c] [$^2H_6$]-DMSO.

from **1e**. The precipitate was washed with ethyl acetate and recrystallized from benzene; m.p. 210–212 °C (Found: C, 73.2; H, 6.9; N, 20.0. $C_{17}H_{18}N_4$ requires C, 73.35; H, 6.52; N, 20.13%); *m/z* 278 (M^+); $\delta_H(CDCl_3)$ 9.78 (1 H, br, NH of **13a**), 7.20 (20 H, m, H_{arom} of **13a** and **13b**), 6.05 (6 H, s, NH_2 for **13a** and **13b**), 4.55 (1 H, br, NH of **13a**), 3.43 (2 H, m, CH_2 of **13b**), 3.16 (2 H, m, CH_2 of **13a**); $\delta_C(CDCl_3)$ 172.07 (C-5 of **13a**), 169.40 (C-3 of **13a**), 159.81 [C-3(5) of **13b**], 135.08 and 134.56 (C-*ipso*), 130.15 and 129.54 (C-*ortho*), 128.47 and 128.27 (C-*meta*), 127.63 and 127.04 (C-*para*), 61.52 (CH_2 of **13a**), 53.15 (CH_2 of **13b**), 43.97 (C-4 of **13a**), 40.98 (C-4 of **13b**).

3-*Amino*-4,4-*dibenzylpyrazol*-5(4H)-*one* **15**. Cyanoacetate **14**[18] (1 g, 38.0 mmol) was added to hydrazine hydrate (0.38 g, 68.0 mmol) and the mixture was heated for 24 h. It was then diluted with water and worked up to give a crude product which was recrystallized from ethanol; yield 80%; m.p. 240–243 °C (lit.,[5] m.p. 242–243 °C) (Found: C, 72.9; H, 6.2; N, 15.0. $C_{17}H_{17}N_3O$ requires C, 73.09; H, 6.13; N, 15.05%); *m/z* 279 (M^+); $\delta_H(CDCl_3)$ 9.42 (1 H, s, NH), 7.19 (10 H, m, H_{arom}), 6.20 (2 H, s, NH_2) and 3.00 (4 H, dd, CH_2); $\delta_C(CDCl_3)$ 173.7 (C-5), 159.4 (C-3), 136.1 (C-6), 129.5 (C-8), 127.6 (C-7), 126.3 (C-9), 56.7 (C-4) and 40.6 (CH_2).

Synthesis of 3-*Halogeno*-4-*alkylpyrazoles: General Procedure*.—These compounds were prepared following a procedure described in ref. 11.

4-*Benzyl*-3-*chloropyrazole* **7**. Isolated by column chromatography on silica gel with dichloromethane and dichloromethane–methanol (99:1) as eluents; yield, 38%, after purification; m.p. 73–75 °C (Found: C, 62.3; H, 4.0; N, 14.2. $C_{10}H_9ClN_2$ requires C, 62.34; H, 4.71; N, 14.54%); *m/z* 193 (M^+) and 194 (M + 1); $\delta_H(CDCl_3)$ 12.06 (1 H, br, NH), 7.56 (1 H, s, CH), 7.26 (5 H, m, H_{arom}) and 3.81 (2 H, s, CH_2).

4-*Benzyl*-3-*bromopyrazole* **8**. Isolated by column chromatography on silica gel with dichloromethane and dichloromethane–methanol (99:1) as eluents; yield 74%; m.p. 78–80 °C (Found: C, 50.4; H, 4.0; N, 11.5. $C_{10}H_9BrN_2$ requires C, 50.66; H, 3.83; N, 11.82%); *m/z* 236 (M^+), 238 (M + 2); $\delta_H(CDCl_3)$ 7.48 (1 H, s, CH), 7.26 (5 H, m, H_{arom}) and 3.79 (2 H, s, CH_2).

Synthesis of 4-*Alkylpyrazoles: General Procedure*.—The appropriate 3,5-diamino-4-alkylpyrazole (3 mmol) was added to 50% aqueous phosphonous acid (9 mmol) and water (5 cm^3) and the mixture cooled at 5 °C. A solution of sodium nitrite (6.6 mmol) in water (2 cm^3) was added dropwise to it and the stirring was continued for 30 min at 5 °C and 4 h at room temperature. After neutralization with 30% aqueous sodium hydroxide, the crude mixture was extracted with diethyl ether. The extract was dried (Na_2SO_4) and evaporated and the residue subjected to column chromatography on silica gel to afford the pure compound.

4-*Benzylpyrazole* **11**. With dichloromethane and dichloromethane–methanol (99:1) as eluents; yield 68%; m.p. 79–80 °C (lit.,[8] oil) (Found: C, 76.0; H, 6.8; N, 17.5. $C_{10}H_{10}N_2$ requires C, 75.92; H, 6.37; N, 17.71%); *m/z* 158 (M^+); $\delta_H(CDCl_3)$ 7.35 (2 H, s, CH), 7.22 (5 H, m, H_{arom}) and 3.82 (2 H, s, CH_2).

4-*Benzyl*-1-*methylpyrazole* **10**. Following the general procedure, the dry ethereal extract was evaporated to afford the oily product; *m/z* 172 (M^+); $\delta_H(CDCl_3)$ 7.25 (5 H, m, H_{arom}), 7.09 (2 H, s, C–H), 3.83 (3 H, s, N–CH_3) and 3.80 (2 H, s, CH_2). This compound was also obtained by the methylation of 4-benzylpyrazole **11**. The picrate derivative, obtained in 76% yield, had m.p. 87–89 °C (Found: C, 51.2; H, 3.6; N, 17.2. $C_{17}H_{15}N_5O_7$ requires C, 50.87; H, 3.77; N, 17.45%).

4-*Phenethylpyrazole* **12**. With dichloromethane, dichloromethane–methanol (90:10) as eluents; yield 40%; m.p. 116–118 °C (lit.,[8] m.p. 94–95 °C) (Found: C, 77.0; H, 7.3; N, 16.2. $C_{11}H_{12}N_2$ requires C, 76.71; H, 7.02; N, 16.27%); *m/z* 172 (M^+); $\delta_H(CDCl_3)$ 7.36 (2 H, s, CH), 7.17 (5 H, m, H_{arom}) and 2.86 (4 H, m, CH_2).

2,2,4-*Tricyanopentan*-3-*one* **4**. 2-Methylmalononitrile **1b** (12 mmol) was added to a solution of hydrazine monohydrate (12 mmol) in ethanol (20 cm^3) and the mixture was refluxed for 4 h. After the mixture had cooled, additional hydrazine hydrate (6 mmol) was added to it and the whole again refluxed for 4 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel with chloroform, chloroform–ethyl acetate and ethyl acetate as eluents to give the product as a reddish oil, which solidified with time; yield 23% after chromatography (Found: C, 60.1; H, 4.3; N, 25.9. $C_8H_7N_3O$ requires C, 59.62; H, 4.38; N, 26.08%); *m/z* 161 (M^+); ν_{max}(KBr)/cm^{-1} 2200 (s, CN) and 1640 (s, C=O); δ_H([$^2H_6$]-DMSO) 3.71 (1 H, q, CH), 3.32 [3 H, s, CH_3–$C(CN)_2$] and 1.39 (3 H, d, CH_3–CH); $\delta_C(CDCl_3)$ 167.52 (C=O), 120.03, 119.61, 114.29 (3 CN), 31.59 (C-1), 24.26 (C-2), 16.23 (C-4) and 15.46 (C-5).

3,5-*Diaminopyrazole* **16** *and* 3,5-*diamino*-4-*bromopyrazole* **17**.

These compounds were prepared according to Settepani and Stokes[19] with similar yields and identical melting points.

3,5-*Diamino*-4-*iodopyrazole* **18**. Using the methods for iodination of pyrazoles of Hüttel *et al.* (iodine/potassium iodide/sodium acetate in water),[20,21] of Morgan and Ackerman (iodine/potassium iodide/sodium acetate in boiling water)[22] and the method used for *p*-iodination of aniline (iodine, sodium hydrogen carbonate in water at 12–15 °C),[23] starting material was partly recovered.

3,5-Diaminopyrazole **16** (1 mmol, 98 mg) reacted with $[IPy_2][BF_4]$ (1.1 mmol, 409 mg)[17] in anhdrous DMSO at room temperature for 5 min to yield **18**. The conversion was total according to the ^{13}C NMR spectrum.

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