A Concise Synthesis of Substituted 4-Alkylaminopyrazolo[3,4-*d*]pyrimidines

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4-Alkylamino-1-methylpyrazolo[3,4-*d*]pyrimidine-3-carbonitriles have been synthesised in 54—81% yields by condensation of *N*-substituted amides with 5-amino-1-methylpyrazole-3,4-dicarbonitrile *via* a Dimroth rearrangement in what is formally an anhydrous medium; the procedure thus permits the synthesis of pyrazolo[3,4-*d*]-pyrimidines with substituents sensitive to hydration.

SEVERAL methods have been described for the elaboration of substituted pyrazolo[3,4-*d*]pyrimidines,[1-3] which as a class exhibit a remarkable variety of biological activities. Certain of these compounds are active against several leukaemias, carcinomas, sarcomas, and tumours.[4] 4-Substituted pyrazolo[3,4-*d*]pyrimidines, for example, are less toxic than their unsubstituted counterparts and therapeutically superior.[4] We describe here a generally applicable two-step synthesis for the production of 4-alkylamino-derivatives. Although we have prepared only certain 1,3,4-trisubstituted and 1,3,4,6-tetrasubstituted pyrazolo[3,4-*d*]pyrimidines, we expect that the use of suitably substituted precursors and appropriate reaction conditions will afford a variety of 2- and 5-substituted derivatives as well.†

The pyrazole (1) is accessible in a single step by treatment of tetracyanoethylene with methylhydrazine.[6] Condensation of this pyrazole with an *N*-substituted amide afforded the substituted pyrazolo[3,4-*d*]pyrimidine

† The question of whether substituents in cyanopyrazoles are on N-1 or N-2 has been investigated.[5] The structures depicted here are consistent with the literature assignments, although definitive proof for the position of the methyl group is at present unavailable.

[1] R. K. Robins in ' Hetercyclic Compounds,' ed. R. C. Elderfield, vol. 8, Wiley, New York, 1967, pp. 406—421, and references therein.

[2] E. C. Taylor and P. K. Loeffler, *J. Amer. Chem. Soc.*, 1960, **82**, 3147.

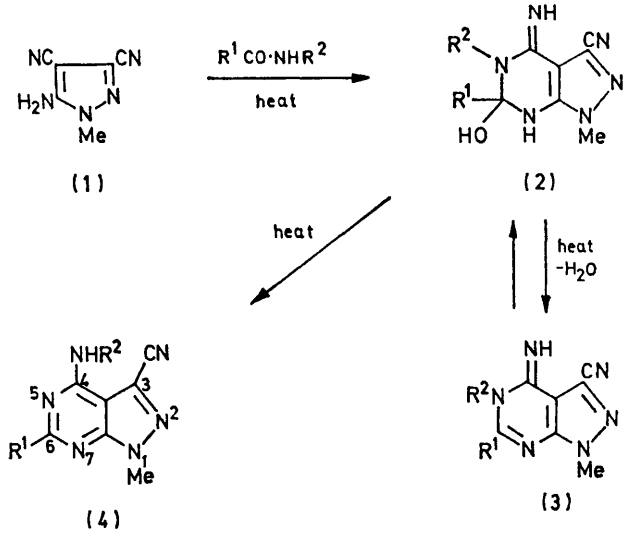
[3] P. Schmidt, K. Eichenberger, M. Wilhelm, and J. Druey, *Helv. Chim. Acta*, 1959, **42**, 763.

[4] (*a*) R. K. Robins, *J. Amer. Chem. Soc.*, 1956, **78**, 784; (*b*) F. R. White, *Cancer Chemother. Rep.*, 1959, **3**, 26; (*c*) J. L. Soctt, jun., and L. V. Foye, *ibid.*, 1962, **20**, 73; (*d*) R. K. Robins, *J. Medicin. Chem.*, 1964, **7**, 186, and references therein.

[5] *E.g.* ref. 3 and P. Schmidt, K. Eichenberger, and J. Druey, *Helv. Chim. Acta*, 1958, **41**, 1052.

[6] C. L. Dickinson, J. K. Williams, and B. C. McKusick, *J. Org. Chem.*, 1964, **29**, 1919, and references therein.

ring system,[3] which is apparently formed *via* the intermediate (2). Species (2) is an obligatory intermediate in the Dimroth rearrangement [2,7] (3) ⟶ (4) and, once formed, may, according to the reaction conditions, be



	R^1	R^2
a;	H	Me
b;	H	Et
c;	Me	Me
d;	H	$[CH_2]_2Pr^i$
e;	H	$CH_2{\cdot}CH{:}CMe_2$
f;	H	$n\text{-}C_6H_{13}$

dehydrated to afford the 5-substituted pyrazolo[3,4-*d*]-pyrimidine (3), or complete the rearrangement to give the 4-substituted pyrazolo[3,4-*d*]pyrimidine (4). Thus one may effect a Dimroth rearrangement in what may be regarded formally as an anhydrous medium. For these compounds the rearrangement can therefore proceed without concomitant hydration of the cyano-group.

In a typical experiment, treatment of the pyrazole (1) with *N*-methylformamide under reflux afforded 62% conversion into the 4-methylaminopyrazolo[3,4-*d*]pyrimidine (4a). Similar reactions with a variety of amides afforded the products indicated in the Table in 54—81% yields.*

Synthesis of 4-substituted pyrazolo[3,4-*d*]pyrimidines

Compound	(4a)	(4b)	(4c)	(4d)	(4e)	(4f)
% Conversion:	62	75	24	66	54	42
% Yield: [a]	66	81	77	66	54	56

[a] Based on consumed starting material.

The conversion (2) ⟶ (4) could be partially hindered by carrying out the reaction in the presence of molecular sieves. This effectively eliminated the equilibrium between (2) and (3) and resulted in the production of both (3) and (4). In the absence of the dehydrating agent, only (4) was formed. Similarly, treatment of the authentic imine (3a) [2] with 1 equiv. of water in *NN*-dimethylformamide at reflux afforded the corresponding 4-substituted pyrazolo[3,4-*d*]pyrimidine (4a). Treatment of (3a) or (4a) with a larger quantity of water in *NN*-dimethylformamide at reflux afforded the corresponding 3-carboxamide. The same compound was obtained when the pyrazole (1) was condensed with *N*-methylformamide in the presence of an excess of water. Conversion of the cyano-group into the corresponding carboxamide could be accomplished by similar procedures in all compounds studied.

The *N*-substituted formamides [8] were synthesised, where necessary, by condensation of the appropriate amines with formic acid, or by treatment of the amines with *N*-formyloxysuccinimide.

EXPERIMENTAL

M.ps were determined on a Thomas Hoover apparatus and are corrected. Elemental analyses were determined by Chemalytics, Inc., or by Scandinavian Microanalytical Laboratory. I.r. spectra were determined on a Perkin-Elmer 457 A spectrophotometer through the courtesy of Professor D. Seyferth. U.v. spectra were determined on a Cary 15 spectrophotometer and mass spectra on a Perkin-Elmer–Hitachi RMU-6 spectrometer using a direct inlet.

Variable amounts of water were associated with different samples of some of these compounds. The water could be removed efficiently only by desiccation under diminished pressure, under which conditions the compounds sublimed. Quantitative u.v. data are not corrected for presumed water of hydration.

N-Alkylformamides.—*N*-Alkylformamides were prepared by either of two methods, as illustrated for *N*-(3-methylbutyl)formamide.

Method A. To 3-methylbutylamine (2·25 g, 3·0 ml, 34·4 mmol), cooled to 0°, was added formic acid (4·5 ml) at a rate which maintained the temperature of the solution below 60°; the solution was then heated at 50° for 5 h. Excess of formic acid was distilled off at atmospheric pressure. The residue was distilled at reduced pressure to afford *N*-(3-methylbutyl)formamide as a liquid (2·24 g, 76%), b.p. 72 °C at 0·15 Torr; *m/e* 115, 100, 86, 72, 58, and 44.

Method B. To *N*-formyloxysuccinimide (7·40 g, 57·6 mmol) was added 3-methylbutylamine (4·50 g, 51·6 mmol) and dioxan (30 ml). The solution was stirred at room temperature for 0·5 h, then refrigerated overnight and concentrated. The residue was distilled as in method A to afford a liquid (2·40 g, 40%).

N-Formyloxysuccinimide.—To dry dioxan (50 ml) was added *N*-hydroxysuccinimide (10·35 g, 90 mmol) and *NN'*-dicyclohexylcarbodi-imide (18·54 g, 90 mmol), followed by formic acid (4·14 g, 90 mmol) dissolved in dioxan (15 ml). The solution was stirred for 0·5 h and filtered. The filtrate was concentrated under diminished pressure and the residue was recrystallized from ethanol to afford white crystals of

* The position of the alkyl substituents in these (4-N) compounds was consistent with their activities in cytokinin bioassays (see *e.g.* F. Skoog and D. J. Armstrong, *Ann. Rev. Plant Physiol.*, 1970, **21**, 359). We thank Professor F. Skoog for the results of the bioassays.

[7] (*a*) N. J. Leonard, S. Achmatowicz, R. N. Loeppky, K. L. Carraway, W. A. H. Grimm, A. Szweykowska, H. Q. Hamzi, and F. Skoog, *Proc. Nat. Acad. Sci. U.S.A.*, 1966, **56**, 709; (*b*) T. Fujii, T. Itaya, C. C. Wu, and F. Tanaka, *Tetrahedron*, 1971, **27**, 2415.

[8] (*a*) A. Furst, W. C. Cutting, and H. Gross, *Cancer. Res.*, 1955, **15**, 294; (*b*) S. Wawzonek and T. P. Culbertson, *J. Amer. Chem. Soc.*, 1960, **82**, 441.

the *ester* (7·6 g, 59%) (Found: C, 41·75; H, 3·9. $C_5H_5NO_4$ requires C, 41·95; H, 3·5%).

The identities of the synthetic *N*-pentyl-, *N*-(3-methylbut-2-enyl)-, *N*-(3-methylbutyl)-, and *N*-hexyl-formamide were confirmed by comparison of physical properties with reported values [8] and analysis of mass spectral data.

4-*Imino*-1,5-*dimethylpyrazolo*[3,4-d]*pyrimidine*-3-*carbonitrile* (3a).[2]—A solution of 5-amino-1-methylpyrazole-3,4-dicarbonitrile (943 mg, 6·4 mmol) in triethyl orthoformate (8 ml) was heated under reflux for 7 h, then concentrated under reduced pressure. The residue was crystallized from absolute ethanol (anhydrous conditions) to afford 5-(ethoxymethyleneamino)-1-methylpyrazole-3,4-dicarbonitrile as white needles (827 mg, 64%), m.p. 98—99°. To a stirred solution of this pyrazole (300 mg, 1·5 mmol) in absolute ethanol (16 ml) was added, in one portion, a suspension obtained from the treatment of methylamine hydrochloride (311 mg, 4·6 mmol) with sodium methoxide (250 mg, 4·6 mmol) in absolute ethanol (4 ml). The mixture was stirred for 15 min at room temperature. Filtration of the resulting suspension afforded a clear liquid which was concentrated under reduced pressure to afford the imine (3a) in quantitative yield, m.p. 175—176° (from methanol); $\lambda_{max.}$ (EtOH) (pH 1) 309sh, 297, 287, 275sh, 244, and 240sh, $\lambda_{min.}$ 291, 256, and 229; $\lambda_{max.}$ (EtOH) (pH 7) 306 and 250, $\lambda_{min.}$ 272 and 235; $\lambda_{max.}$ (EtOH) (pH 12) 290 and 251, $\lambda_{min.}$ 273 and 232 nm; $\nu_{max.}$ (KBr) 3300, 3160, 2220, 1625, and 1575 cm^{-1}.

The same product was obtained when a solution of the dinitrile (247mg, 1·6 mmol) (1) in *N*-methylformamide (5 ml) was heated under reflux over molecular sieves for 2 h.

1-*Methyl*-4-*methylaminopyrazolo*[3,4-d]*pyrimidine*-3-*carbonitrile* (4a).—To the dinitrile (1) (247 mg, 1·68 mmol) was added anhydrous *N*-methylformamide (3 ml). The solution was heated at reflux under nitrogen for 2 h, cooled, concentrated, and applied to a column of silica gel (2 × 10 cm). Elution with a chloroform–ethyl acetate gradient afforded compound (1) (17 mg) (20% ethyl acetate), followed by the desired *product* (4a) (ethyl acetate); yield 195 mg [66% based on consumed (1a); 62% conversion], m.p. 274—275° (sublimation); $\lambda_{max.}$ (EtOH) (pH 1) 318 nm (ε 13,600), 308 (15,200), 299sh, 281 (8300), 270sh, 250sh, and 231sh, $\lambda_{min.}$ 315 (12,100), 283 (8200), and 239 (5000); $\lambda_{max.}$ (EtOH) (pH 7) 314 (9800), 266sh, 253 (7900), and 227 (11,500), $\lambda_{min.}$ 283 (4500) and 242 (6700); $\lambda_{max.}$ (EtOH) (pH 12) 310 (9400), 280sh, 262 (8800), and 235sh, $\lambda_{min.}$ 288 (6500) and 240 nm (6200); *m/e* 188, 173, 161, 160, 159, and 158; $\nu_{max.}$ (KBr) 3480, 3050, 3000—2900, 1640, and 1590 cm^{-1} (Found: C, 50·75; H, 4·35. $C_8H_8N_6$ requires C, 51·05; H, 4·3%).

Rearrangement of the Imine (3a) *to the Alkylamine* (4a).—To a suspension of the imine (3a) (53 mg, 0·28 mmol) in *NN*-dimethylformamide (3 ml) was added water (2 drops). The mixture was heated at 190° for 4 h, cooled, and concentrated under reduced pressure to afford a residue which contained both (3a) and the rearrangement product (4a). Small amounts of 1-methyl-4-methylaminopyrazolo[3,4-*d*]-pyrimidine-3-carboxamide were also in evidence.

4-*Ethylamino*-1-*methylpyrazolo*[3,4-d]*pyrimidine*-3-*carbonitrile* (4b).—To the dinitrile (1) (248 mg, 1·69 mmol) was added anhydrous *N*-ethylformamide (5 ml). The solution was heated under reflux under nitrogen for 5·5 h, cooled, and concentrated under reduced pressure. The residue was chromatographed on Sephadex LH-20 (elution with water) and then on neutral silica gel (elution with ether) to afford white *crystals* (4b) (200 mg, 75%; 81% based on consumed starting material), m.p. 139—141°; $\lambda_{max.}$ (EtOH) (pH 1) 321 (ε 11,700), 309 (13,100), 301sh, 281 (7900), 256 (6400), and 231 (8500), $\lambda_{min.}$ 317 (10,200), 285 (7700), 262 (6400), 245 (6100), and 220 (8100); $\lambda_{max.}$ (EtOH) (pH 7) 317 (8000), 253 (8100), and 231 (12,600), $\lambda_{min.}$ 285 (4600) and 245 (7300); $\lambda_{max.}$ (EtOH) (pH 12) 313 (9600), 262 (8600), and 246 (7900), $\lambda_{min.}$ 289 (6000), 252 (7600), and 242 nm (7700); *m/e* 202, 187, 175, 174, 159, 158, and 147; $\nu_{max.}$ (Nujol) 3300, 2960—2850, 2240, 1615, and 1565 cm^{-1} (Found: C, 52·45; H, 4·8. $C_9H_{10}N_6$,0·25H_2O requires C, 52·3; H, 5·1%).

1,6-*Dimethyl*-4-*methylaminopyrazolo*[3,4-d]*pyrimidine*-3-*carbonitrile* (4c).—A solution of the dinitrile (1) (270 mg, 1·84 mmol) in *N*-methylacetamide (5 ml) was heated under reflux for 10 h, cooled, and concentrated under reduced pressure. Chromatography of the product on a silica gel column (2 × 17 cm) (elution with a chloroform–ethyl acetate gradient) afforded the starting pyrazole (182 mg) (50% ethyl acetate), followed by the *product* (4c) (93 mg, 24%; 77% based on consumed starting material), m.p. 158—158·5°; $\lambda_{max.}$ (EtOH) (pH 1) 248 (ε 7400), $\lambda_{min.}$ 233 (6400); $\lambda_{max.}$ (EtOH) (pH 7) 290 (3800) and 242 (8200), $\lambda_{min.}$ 269 (3000) and 230 (7600); $\lambda_{max.}$ (EtOH) (pH 12) 293 (4000) and 242 (8700), $\lambda_{min.}$ 269 (3000) and 232 nm (8200); *m/e* 202, 173, and 147 (Found: C, 49·5; H, 5·8. $C_9H_{10}N_6$,H_2O requires C, 49·05; H, 5·5%).

1-*Methyl*-4-(3-*methylbutylamino*)*pyrazolo*[3,4-d]*pyrimidine*-3-*carbonitrile* (4d).—A solution of the dinitrile (1) (175 mg, 1·19 mmol) in *N*-(3-methylbutyl)formamide (2·5 ml) was heated under reflux for 1 h. Excess of amide was removed under reduced pressure and the residue was chromatographed on neutral silica gel (elution with ether) to afford white *crystals* (4d) (192 mg, 66%), m.p. 100—102°; $\lambda_{max.}$ (EtOH) (pH 1) 322 (ε 16,000), 311 (17,900), 281 (8700), 272sh, 259 (6600), and 233sh, $\lambda_{min.}$ 318 (14,500), 285 (8300), 260 (6600), and 241 (5700); $\lambda_{max.}$ (EtOH) (pH 7) 320 (10,700), 255 (8300), and 230 (12,800), $\lambda_{min.}$ 285 (4000), 243 (5700), and 212 (10,000); $\lambda_{max.}$ (EtOH) (pH 12) 314 (11,100) and 263 (10,400), $\lambda_{min.}$ 290 (7300) and 244 nm (7900); *m/e* 244, 229, 201, 188, 174, 149, and 147; $\nu_{max.}$ (Nujol) 3400, 2960—2850, 2240, 1615, and 1560 cm^{-1} (Found: C, 56·6; H, 7·15. $C_{12}H_{16}N_6$,0·5H_2O: C, 56·9; H, 6·75%).

1-*Methyl*-4-(3-*methylbut*-2-*enylamino*)*pyrazolo*[3,4-d]-*pyrimidine*-3-*carbonitrile* (4e).—A solution of the dinitrile (1) (38 mg, 0·26 mmol) and *N*-(3-methylbut-2-enyl)formamide (1·0 g) was heated under reflux for 45 min. Excess of amide was removed at *ca.* 0·2 Torr and 120°. The residue was purified on Sephadex LH-20 (elution with water) to yield white *crystals* (4e) (38·9 mg, 54%), m.p. 117—119°; $\lambda_{max.}$ (EtOH) (pH 1) 322 (ε 8900), 311 (9900), 283sh, 271sh, and 249 (3600), $\lambda_{min.}$ 318 (8700), 261 (3600), and 240 (3400); $\lambda_{max.}$ (EtOH) (pH 7) 317 (6600), 254 (5300), and 229 (7800), $\lambda_{min.}$ 286 (2500), 244 (4700), and 217 (7000); $\lambda_{max.}$ (EtOH) (pH 12) 314 (7000) and 262 (6600), $\lambda_{min.}$ 290 (4900) and 244 nm (5300); $\nu_{max.}$ (Nujol) 3410, 2980—2850, 2230, and 1610 (Found: C, 59·3; H, 5·75. $C_{12}H_{14}N_6$ requires C, 59·5; H, 5·8%).

4-*Hexylamino*-1-*methylpyrazolo*[3,4-d]*pyrimidine*-3-*carbonitrile* (4f).—A solution of the dinitrile (1) (263 mg, 1·79 mmol) in *N*-hexylformamide (4·9 g) was heated under reflux for 1 h. The residue remaining after removal of excess of amide under reduced pressure was chromatographed on silica gel (elution with ethyl acetate) to afford white *crystals* (4f) (194 mg, 42%; 56% based on consumed starting material), m.p. 75—77°; $\lambda_{max.}$ (EtOH) (pH 1) 322

(ε 13,300), 311 (15,300), 302sh, 281 (7800), 272sh, 249 (5900), and 232sh, $\lambda_{min.}$ 318 (12,000), 285 (7600), 254 (5700), and 241 (5600); $\lambda_{max.}$ (EtOH) (pH 7) 317 (9600), 254 (8000), and 228 (11,500), $\lambda_{min.}$ 285 (3900), 243 (7000), and 213 (9000); $\lambda_{max.}$ (EtOH) (pH 12) 312 (9400) and 262 (9200), $\lambda_{min.}$ 290 (6600) and 243 nm (7000); *m/e* 258, 243, 229, 215, 201, 188, 174, and 147; $\nu_{max.}$ (film) 3400, 2960—2860, 2230, and 1600 cm^{-1} (Found: C, 59·75; H, 6·9. $C_{13}H_{18}N_6,0·25H_2O$ requires C, 59·4; H, 7·1%).

Conversion of the Nitrile into 4-*Hexylamino*-1-*methylpyrazolo*-[3,4-d]*pyrimidine*-3-*carboxamide*.—This reaction was typical of the hydration of compounds (4a—f). To the nitrile (4f) (30 mg, 1·2 mmol) was added concentrated ammonium hydroxide solution (5 ml). The suspension was heated at 70° for 2 h. The resulting solution was concentrated under reduced pressure and the solid residue was crystallized from methanol to afford white crystals of the *carboxamide* (23 mg, 70%), m.p. 258—259° (Found: C, 56·3; H, 7·1. $C_{13}H_{20}N_6O$ requires C, 56·5; H, 7·3%).

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