Allenes. Part 43.[1] A Novel Synthesis of Pyrimidines of Potential Pharmaceutical Interest from Allenic Nitriles.

Stephen R. Landor* and Phyllis D. Landor
Chemistry Department, University of the West Indies, Kingston 7, Jamaica
V. E. Williams
University of Lagos, Lagos, Nigeria

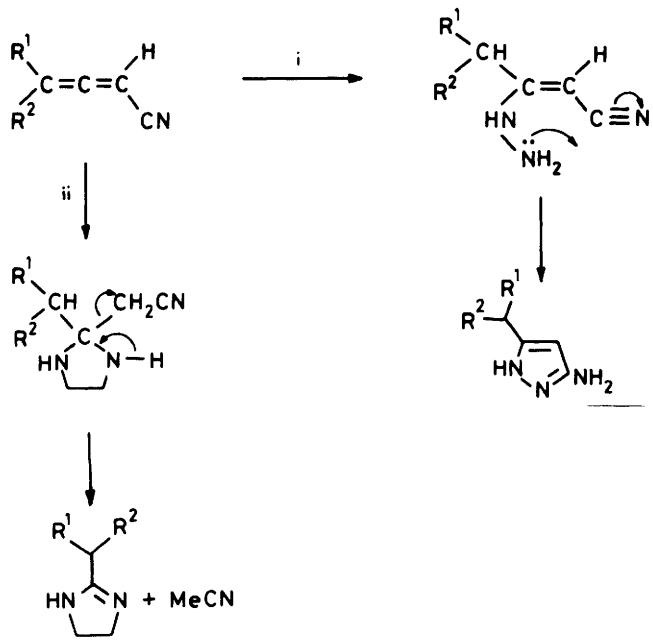
The reactions of 4,4-dialkylbuta-2,3-dienenitriles and 3-phenylpropynenitrile with guanidine and acetamide have been investigated; a number of 6-alkyl-2,4-diaminopyrimidines and 6-alkyl-2-methyl-4-aminopyrimidines as well as 2,4-diamino-6-phenylpyrimidine and 4-amino-2-methyl-6-phenylpyrimidine have been synthesised.

Pyrimidines form a large group of biologically active compounds, and 2,4-diaminopyrimidines in particular have high antimalarial activity.[2] Our recent work on the synthesis of various heterocycles[3] from allenic nitriles led us to investigate a possible pyrimidine synthesis.

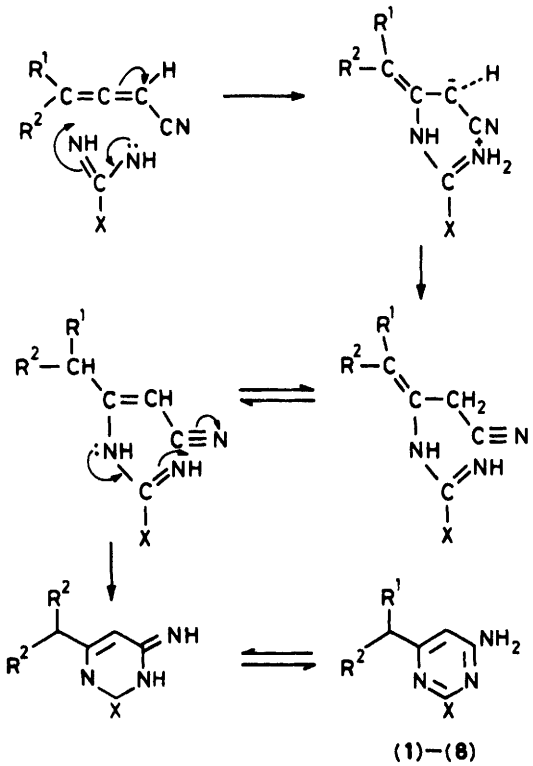
We have previously shown (Scheme 1) that 1,2-dinucleophiles *e.g.* hydrazine, first add in the Michael position to give adducts and then cyclise by nucleophilic attack on the carbon of the nitrile to give pyrazoles,[4] on the other hand, 1,4-dinucleophiles, *e.g.* diaminoethane, give a double Michael addition with elimination of acetonitrile to give imidazolines.[5] We therefore expected that 1,3-dinucleophiles such as amidines would follow a similar pathway to hydrazine, to give the six-membered pyrimidine rings.

In the event, the reaction of 4,4-dialkylallenyl nitriles with guanidine or acetamidine gave 6-substituted 2,4-diamino- and 2-methyl-4-amino-pyrimidines as outlined in Scheme 2. The reaction between the allenic nitrile and the amidine was best carried out with sodium hydroxide in 95% ethanol under reflux for 1—2 h (see Table). The 2,4-diaminopyrimidines showed $\lambda_{max.}$ 281—282 nm and the 4-amino-2-methylpyrimidines $\lambda_{max.}$ 268—271 nm. The n.m.r. spectra showed a characteristic signal at δ *ca.* 6.0 for the heterocyclic =CH group as well as signals for the substituent groups of the pyrimidines. The i.r. spectra gave typical NH stretching bands at about 3 500 and 3 300, NH deformation bands at 1 650 and 1 640, and an aromatic C=C stretch at 1 600 cm^{-1}.

In a similar manner 3-phenylpropynenitrile with guanidine or acetamidine gave 6-phenyl substituted pyrimidines (Scheme 3) with the expected i.r. and n.m.r. spectra (*cf.* Experimental



Scheme 1. *Reagents:* i, NH_2NH_2; ii, $NH_2CH_2CH_2NH_2$



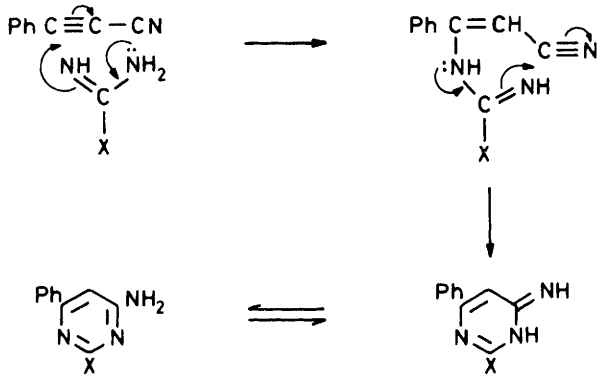
	R^1	R^2	X
(1)	Me	Me	NH_2
(2)	Me	Me	Me
(3)	Me	Et	NH_2
(4)	Me	Et	Me
(5)	Et	Et	NH_2
(6)	Et	Et	Me
(7)	Me	Bu^t	NH_2
(8)	Me	Bu^t	Me

Scheme 2.

Table. Preparation of pyrimidines

Compound	M.p. (°C)	Base[a]	Time (h)	Yield[d]	$\lambda_{max.}$(nm)	ε
(1)	134	A	1	11	232	8 700
		B	5	2[b]	281	7 700
(2)	96	A	1	10	234	9 400
		B	5	19[b]	270	3 800
(3)		A	1	53[c]	233	5 300
					282	4 400
(4)	112	B	5	69[b]	234	11 200
					270	4 500
(5)	147	A	2	46	232	10 500
		B	8	19[b]	281	8 500
		C	2	8		
(6)	138	A	2	82	233	9 100
					268	3 500
(7)	140	A	2	60	232	9 800
					282	7 400
(8)	163	A	2	55	233	19 100
					271	6 800

[a] A NaOH–EtOH; B K_2CO_3–95% EtOH; C Na^+O^-Et–EtOH. [b] Column chromatography on neutral alumina. [c] Crude crystalline material. [d] All pyrimidines gave the expected n.m.r. signals and the correct value for *m/z* in the mass spectrum.



Scheme 3. X = NH_2 or Me

section); the u.v. signals were shifted to longer wavelengths to give $\lambda_{max.}$ 287 nm for the 4-amino-2-methyl compound and $\lambda_{max.}$ 307 nm for the 2,4-diamino compound.

Experimental

I.r. spectra were determined with a Perkin-Elmer 257 spectrophotometer. U.v. spectra were obtained for ethanolic solutions with a Unicam 800 spectrometer. N.m.r. spectra were determined with a Varian T60 spectrometer for solutions in deuteriochloroform, unless otherwise stated, with tetramethylsilane as internal standard. The allenic nitriles were prepared as previously described.[6] Ether refers to diethyl ether.

2,4-*Diamino*-6-(1-*ethylpropyl*)*pyrimidine* (**5**).—(*a*) Guanidine hydrochloride (3.3 g, 0.034 mol) was dissolved in alcoholic sodium hydroxide (2.6 g in 40 ml of 95% ethanol) and 4-ethylhexa-2,3-dienenitrile (3.6 g, 0.03 mol) in ethanol (4 ml) was added dropwise to the mixture with vigorous stirring. The precipitated sodium chloride was filtered off and the filtrate refluxed for 2 h. The solvent was removed and the crude product extracted into ether. The ethereal layer was extracted with dilute hydrochloric acid (3 × 40 ml), the acid layer made alkaline with 2N-sodium hydroxide, and the pyrimidine extracted back into ether (3 × 40 ml) and dried ($MgSO_4$). Removal of solvent and recrystallisation from chloroform gave 2,4-*diamino*-6-(1-*ethylpropyl*)*pyrimidine* (2.5 g, 46%), m.p. 145 °C (Found: C, 60.0; H, 9.0; N, 31.2. $C_9H_{16}N_4$ requires C, 60.0; H, 8.9; N, 31.1%; $\nu_{max.}$ 3 500, 3 300 (NH), 1 650, 1 640 (NH deform), and 1 600 cm^{-1} (Ar, C=C); $\lambda_{max.}$ 232 (10 500) and 281 nm (ε 8 500); δ 0.80 (6 H, t, CH_3CH_2), 1.59 (4 H, quint., CH_2CH_3) 2.15 (1 H, quint., Et_2CH), 4.83 (2 H, br s, NH_2 disappears on deuteriation), 5.03 (2 H, br s, NH_2 disappears on deuteriation), and 5.65 (1 H, s, =CH).

(*b*) 4-Ethylhexa-2,3-dienenitrile (4.8 g, 0.04 mol), guanidine hydrochloride (4.4 g, 0.046 mol), and anhydrous potassium carbonate (6.3 g, 0.046 mol) were refluxed in ethanol (30 ml) for 8 h. The reaction mixture was cooled, the solid (KCl + K_2CO_3) was filtered off and washed with cold ethanol (20 ml). The filtrate was evaporated, chloroform (30 ml) added, and the whole washed with water. The chloroform layer was dried ($MgSO_4$) and evaporated to give the crude pyrimidine (2 g, 28%) containing unchanged starting materials, (*ca.* 50% from $\lambda_{max.}$ 280 nm, ε 4 200). Chromatography on neutral alumina (35 g, grade 1, deactivated with 2 ml of water) gave, on elution with chloroform, 2,4-diamino-6-(1-ethylpropyl)pyrimidine (**5**) (1.4 g, 19%) with similar spectroscopic data to the sample obtained in (*a*).

(*c*) Sodium ethoxide [from sodium (0.83 g, 0.036 g-atom) in absolute ethanol (50 ml)] and guanidine hydrochloride (3.3 g, 0.034 mol) were mixed by stirring and then 4-ethylhexa-2,3-dienenitrile (3.6 g, 0.03 mol) was added dropwise. A precipitate of sodium chloride was filtered off and the filtrate was refluxed for 2 h. Work-up as in (*a*) gave impure 2,4-diamino-6-(1-ethylpropyl)pyrimidine (**5**) (1.5 g, equivalent to 8%, as determined from the u.v. absorption at $\lambda_{max.}$ 280 nm). Data for this compound and for the pyrimidines (**1**), (**3**), and (**7**) prepared by methods (*a*), (*b*), and (*c*) are given in the Table. Acetamidine hydrochloride was used to prepare pyrimidines (**2**), (**4**), (**6**), and (**8**), in a similar manner.

2,4-*Diamino*-6-*phenylpyrimidine*.—3-Phenylpropynenitrile[5,7] (2.54 g, 0.02 mol), guanidine hydrochloride (1.91 g, 0.02 mol), and anhydrous potassium carbonate (2.7 g, 0.02 mol) were refluxed in ethanol (30 ml) for 5 h and then cooled. The reaction mixture was filtered to remove inorganic salts and evaporated under reduced pressure. Ether (30 ml) was added to the residue, the whole extracted with 1M-HCl (8 × 50 ml), then made strongly alkaline by the addition of NaOH and the product extracted into chloroform (10 × 100 ml). The chloroform layer was washed with water (3 × 100 ml), dried ($MgSO_4$–Na_2CO_3), and evaporated to give the crude pyrimidine. This was dissolved in glacial acetic acid (25 ml), diluted with water (75 ml), warmed, treated with active charcoal, filtered, and made strongly alkaline (2M-NaOH). Refrigeration gave 2,4-*diamino*-6-*phenylpyrimidine* (2.0 g, 54%), m.p. 160—161 °C (Found: C, 64.7; H, 5.5; N, 29.9. $C_{10}H_{10}N_4$ requires C, 64.5; H, 5.4; N, 30.1%); $\nu_{max.}$(Nujol) 3 400, 3 340 (NH), 1 635 (NH deform), and 1 600 cm^{-1} (Ar C=C); $\lambda_{max.}$ 239 (24 700) and 307 nm (6 900); δ[$(CD_3)_2SO$] 4.80 (4 H, br s, NH_2 disappears on deuteriation), 6.24 (1 H, s, =CH), 7.22—7.6 (3 H, m, 3, 4, 5 ArH), and 7.7—8.0 (2 H, m, 2, 6 ArH); *m/z* 186 ($C_{10}H_{10}N_4$ requires *M* 186).

4-*Amino*-2-*methyl*-6-*phenylpyrimidine*.—3-Phenylpropynenitrile (2.54 g, 0.02 mol), acetamidine hydrochloride (1.89 g, 0.02 mol), anhydrous potassium carbonate (2.7 g, 0.02 mol), and ethanol (30 ml) similarly gave 4-*amino*-2-*methyl*-6-*phenylpyrimidine* (1.95 g, 53%), m.p. 163—164 °C (Found: C, 71.5; H, 6.1; N, 22.4. $C_{11}H_{11}N_3$ requires C, 71.35; H, 5.95; N, 22.7%); $\nu_{max.}$ 3 380, 3 280 (NH), 1 670 (NH deform), 1 625, and 1 600 cm^{-1} (Ar C=C); $\lambda_{max.}$ 239 (25 700) and 287 (5 900); δ[$(CD_3)_2SO$] 2.52

(3 H, s, CH_3), 5.89 (2 H, br s, NH_2, disappears on deuteriation), 6.65 (1 H, s, =CH), 7.3—7.5 (3 H, m, 3, 4, 5 ArH), and 7.8—8.0 (2 H, m, 2, 6, ArH); *m/z* 185 ($C_{11}H_{11}N_3$ requires *M* 185).

Acknowledgements

We wish to thank V. I. Ekhato and F. O. Adenubi for experimental assistance during their third year projects at the University of Lagos.

References

1 Part 42, Z. T. Fomum, P. F. Asobo, S. R. Landor, and P. D. Landor, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1079.
2 P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, 1951, **73**, 3763.
3 S. R. Landor, 'The Chemistry of the Allenes,' Academic Press, New York and London, 1982, vol. 2, ch. 5.
4 Z. T. Fomum, S. R. Landor, P. D. Landor, and G. W. B. Mpango, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2997.
5 S. R. Landor, P. D. Landor, Z. T. Fomum, and G. W. B. Mpango, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2289.
6 P. M. Greaves, S. R. Landor, and D. J. R. Laws, *J. Chem. Soc. C*, 1968, 291.
7 A. M. Sladkov and A. Y. Ukhim, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1964, 384.

Received 21*st November* 1983; *Paper* 3/2062