Tetrahedron Vol. 39, No. 19, pp. 3197 to 3199, 1983
Printed in Great Britain.

0040–4020/83 $3.00 + .00
Pergamon Press Ltd.

REACTIONS WITH α-SUBSTITUTED CINNAMONITRILES

A NOVEL SYNTHESIS OF ARYLPYRIMIDINES

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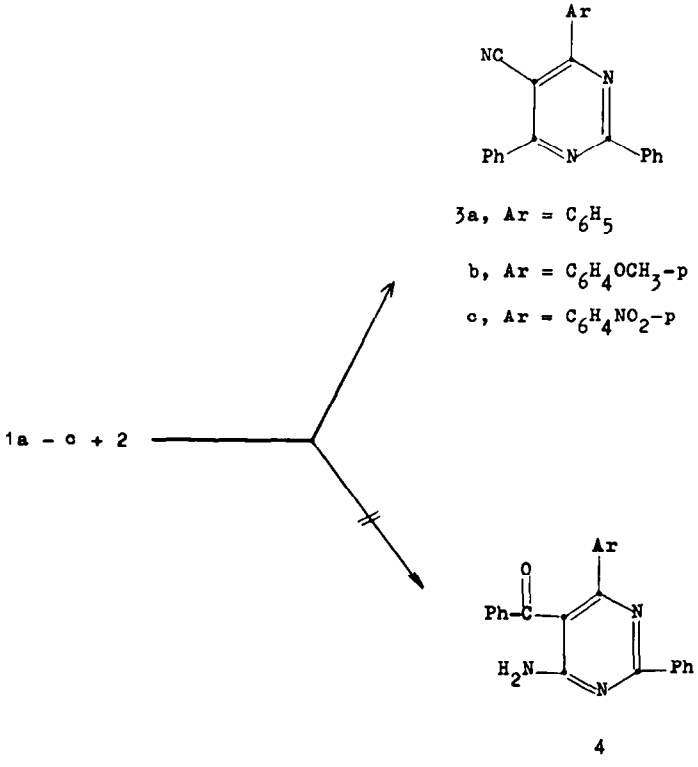
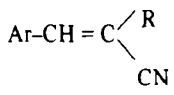
(*Received in UK 13 January* 1983)

Abstract—α-Benzoyl- and α-ethoxycarbonylcinnamonitrile derivatives **1a–c** and **1d–f** reacted with benzamidine hydrochloride (**2**) in boiling pyridine to give the fully aromatized aryl-pyrimidine derivatives **3a–c** and **6a–c** respectively. In contrast the α-cyanocinnamonitrile derivatives **1g–j** reacted with **2** under the same conditions to form the dihydropyrimidine derivatives **7a–d**. Compounds **7a,b** could be dehydrogenated to the fully aromatized analogues **8a,b** as hydrobromide salts by treatment with bromine in acetic acid. The free basic compound **8a** was isolated from **8a.HBr** by neutralisation. A scheme for the reaction steps of 1 and 2 is proposed and the structures of the synthesised compounds were proved by chemical methods and spectral studies.

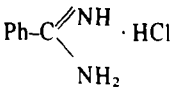
Pyrimidine derivatives are used on a large scale in medicine as antitumor[1] agents, analgesics,[2] bactericides,[3] and fungicides,[4] and in agriculture as plant growth stimulators.[5] We report a novel, simple and convenient method for the synthesis of arylpyrimidine derivatives, by the reaction of α-substituted cinnomonitrile derivatives (**1a–j**) with benzamidine hydrochloride (**2**). Thus, it has been found that the reaction of equimolecular amounts afford products for which structures **3** and **4** seem possible, but structure **3** was based on analytical



and spectral data.



1a, Ar = C_6H_5; R = COC_6H_5
b, Ar = $C_6H_4OCH_3$-p; R = COC_6H_5
c, Ar = $C_6H_4NO_2$-p; R = COC_6H_5
d, Ar = C_6H_5; R = $CO_2C_2H_5$
e, Ar = $C_6H_4OCH_3$-p; R = $CO_2C_2H_5$
f, Ar = $C_6H_4NO_2$-p; R = $CO_2C_2H_5$
g, Ar = C_6H_5; R = CN
h, Ar = $C_6H_4OCH_3$-p; R = CN
i, Ar = $C_6H_4NO_2$-p; R = CN
j, Ar = C_6H_4Cl-o; R = CN



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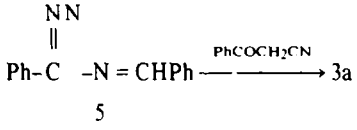
The IR† spectrum of **3a** showed an absorption band at 2220 (CN) and no bands in both (C=O) and (NH) regions. Its PMR spectrum displayed signals at 7.8 (m, 10H, aromatic protons), 8.26 (m, 3H, aromatic protons) and 8.75 (m, 2H, aromatic protons). Compound **3a** could also be synthesised by the reaction of benzalbenzamidine[6] **5** with benzoylacetonitrile.

Similar to the behaviour of the **1a–c**, compounds **1d–f** react with **2** to give the 4-aryl-5-cyano-6-oxo-2-phenyl-1,6-dihydropyrimidine derivatives (**6a–c**), the structure of which was based on analytical and spectral studies (*cf* Experimental).



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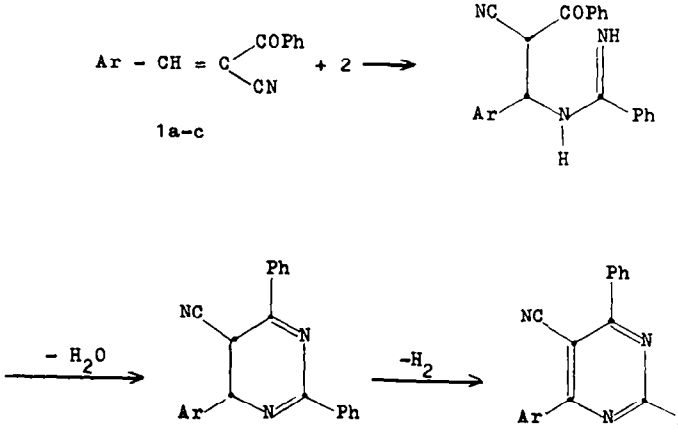
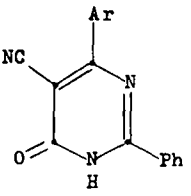
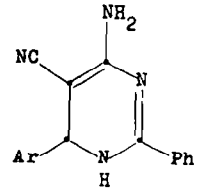
The formation of **3** may be formed as in Scheme A.



Scheme A.



6a, Ar = C_6H_5
b, Ar = $C_6H_4OCH_3$-p
c, Ar = $C_6H_4NO_2$-p



7a, Ar = C_6H_5
b, Ar = $C_6H_4OCH_3$-p
d, Ar = C_6H_4Cl-o

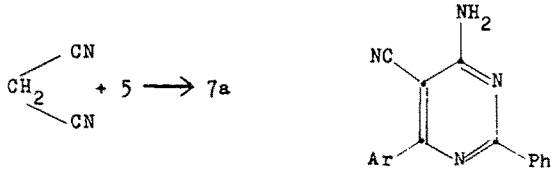
data. Thus, the PMR spectrum of **7a**, showed a singlet at 3.61 attributed to the presence of pyrimidine H-6, while its IR spectrum showed characteristic absorption bands (Experimental). Further confirmation of the structure of **7a** was made by a comparison with an authentic sample prepared from malononitrile and **5**. In addition, compounds **7a,b** were dehydrogenated,[7,8] to give 4-amino-6-aryl-5-cyano-2-phenylpyrimidine derivatives (**8a,b**) as their hydrobromide salts. The free base **8a** was isolated by neutralisation (Na_2CO_3) of 8a.HBr. The PMR spectrum of **8a.HBr** showed no shifts at the higher field region (up to 7 ppm) indicating pyrimidine H-6 was intirely absent (*cf* Experimental).

In contrast to **1a–f**, compounds **1g–j** reacted with **2** under the same experimental conditions to give the 4 - amino - 6 - aryl - 5 - cyano - 2 - phenyl - 1,6 - dihydropyrimidine derivatives (7a–d).

The structures are based on analytical and spectral

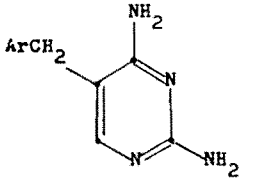
A somewhat analogous synthesis of 2,4-diamino-5-benzylpyrimidine derivatives (**10**) from α-arylmethyl-B-alkoxyacrylonitriles and guanidine was reported by Tokuyama.[9]

† ν_{max} in cm^{-1} and PMR chemical shifts in δ ppm throughout the paper.



8a, Ar = C_6H_5

b, Ar = $C_6H_4OCH_3$-p



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EXPERIMENTAL

M.ps are uncorrected. IR spectra were determined as KBr pellets with a Pye-Unicam SP 100 spectrophotometer. PMR spectra were determined (in DMSO-d_6) with a Varian A-60 spectrophotometer.

4-Aryl-5-cyano-2,6-diphenylpyrimidines **3a–c**

General procedure. A mixture of 1.8 g of **2**, 20 ml of pyridine and an equimolecular amount of each of **1a–c** was refluxed for 5 hr. The mixture was cooled and poured into cold water. The ppt was collected and crystallised from the appropriate solvent.

Compound **3a** was obtained in 82% yield and crystallised from dioxan m.p. 255°: IR 2220 (C ≡ N), 1530 (C=N); δ 7.8 (m, 10H, aromatic protons), 8.26 (m, 3H, aromatic protons) and 8.75 (m, 2H, aromatic protons). Calc for $C_{23}H_{15}N_3$: C, 82.85; H, 4.53; N, 12.62. Found: C, 82.7; H, 4.6; N, 12.6%.

Compound **3b** was crystallised from benzene-n-hexane in 80% yield, m.p. 155°: IR 2230 and 1515. Calc for $C_{24}H_{17}N_3O$: C, 79.31; H, 4.71; N, 11.57. Found: C, 79.4; H, 4.7; N, 11.3%.

Compound **3c** was crystallised from AcOH in 75% yield, m.p. 260°: IR 2220 and 1520. Calc for $C_{23}H_{14}N_4O_2$: C, 73.0; H, 3.73; N, 14.82. Found: C, 73.2; H, 3.9; N, 14.7%.

4-Aryl-5-cyano-6-oxo-2-phenyl-1,6-dihydropyrimidines **6a–c**

A mixture of equimolecular amounts of **2** and each of **1d–f** was boiled in pyridine. The soln was treated in a manner similar to that applied inthe synthesis of **3**.

Compound **6a** was crystallised from dioxan in 78% yield, m.p. 255°: IR 3225 (NH), 2220 (C ≡ N), 1670 (CO) and 1535 (C=N); δ 7.8 (m, 10H, aromatic protons), 8.18 (m, 3H, aromatic protons), 8.4 (m, 2H, aromatic protons) and 8.9 (broads, 1H, NH). Calc for $C_{17}H_{11}N_3O$: C, 74.7; H, 4.05; N, 15.39. Found: C, 74.5; H, 4.0; N, 15.2%.

Compound **6b** was crystallised from EtOH in 67% yield, m.p. 80°: IR 3200 (NH), 2220 (C ≡ N), 1670 (CO) and 1540 (C=N). Calc for $C_{18}N_{13}N_3O_2$: C, 71.27; H, 4.32; N, 13.87. Found: C, 71.2; H, 4.2; N, 13.9%.

Compound **6c** was obtained in 71% yield and crystallised from dilute EtOH, m.p. 125°: IR 3205 (NH), 2215 (C ≡ N), 1690 (CO) and 1560 (C=N). Calc for $C_{17}H_{10}N_4O_3$: C, 64.14; H, 3.16; N, 17.62. Found: C, 64.3; H, 3.0; N, 17.5%.

†The NH_2 and NH prptons could not be observed due to the rapid intermolecular exchange between these protons and DHO contaminated with the solvent.[10]

4-Amino-6-aryl-5-cyano-2-phenyl-1,6-dihydropyrimidine derivatives **7a–d**

General procedure. About 2 g of **2** were dissolved in 50 ml pyridine. An equimolecular amount of each of **1g–j** was added and the soln was refluxed for 5 hr, left to cool and poured into cold water. The ppt, dried and crystallised from the appropriate solvent.

Compound **7a**† was crystallised from dioxan in 87% yield, m.p. 212°: IR 3480, 3400, 3350, 3225 (NH); 3050, 2960, 2925 (CH); 2220 (CN) and 1650 (NH_2); δ 3.61 (s, 1H, CH); 7.68 (m, 5H, aromatic protons); 8.05 (m, 3H, aromatic protons); and 8.48 (m, 2H, aromatic protons). Calc for $C_{17}H_{14}N_4$: C, 74.42; H, 5.14; N, 2044. Found: C, 74.5; H, 5.1; N, 20.2%.

Compound **7b** was obtained in 83% yield and crystallised from EtOH, m.p. 197°: IR 3450, 3400, 3345, 3210 (NH); 3050, 2950, 2930 (CH); 2220 (CN) and 1645 (NH_2). Calc for $C_{18}H_{16}N_4O$: C, 71.03; H, 5.29; N 18.42. Found: C, 71.1; H, 5.2; N, 18.6%.

Compound **7c** was crystallised from EtOH in 72% yield, m.p. 215: IR 3460, 3400, 3340, 3220 (NH); 3065, 2950, 2915 (CH); 2220 (CN) and 1650 (NH_2). Calc for $C_{17}H_{13}N_4O_2$: C, 63.93; H, 4.10; N, 21.95. Found: C, 64.0; H, 4.2; N, 21.8%.

Compound **7d** was obtained in 76% yield, m.p. 196°: IR 3450, 3405, 3350 (NH); 3060, 2950, 2920 (CH); 2220 (CN) and 1650 (NH_2). Calc for $C_{17}H_{13}ClN_4$: C, 66.11; H, 4.24; Cl, 11.49; N, 18.16. Found: C, 66.3; H, 4.3; Cl, 11.6; N, 18.0%.

4-Amino-6-aryl-5-cyano-2-phenylpyrimidine hydrobromide derivatives **8a,b**

Each of **7a,b** (1 g) was dissolved in 50 ml AcOH. An excess (1.5 moles) of Br_2 in 20 ml AcOH was added gradually, and the soln was heated at 100° for 3 hr, left to cool and poured into water. The ppt was collected, dried, and crystallised from dioxan.

Compound **8a.HBr** was obtained in 90% yield, m.p. 217 (charing): IR 3480, 3350, 3245 (NH); 2215 (C ≡ N); 1655 (NH_2) and 1540 (C=N); δ 7.69 (m, 6H, NH and aromatic protons), 8.07 (m, 3H, aromatic protons) and 8.5 (m, 2H, aromatic protons). Calc for $C_{17}H_{13}BrN_4$: C, 57.78; H, 3.70; Br, 22.64; N, 15.87. Found: C, 57.9; H, 3.7; Br, 22.4; N, 15.7%.

Compound **8b.HBr** was obtained in 86% yield, m.p. 208° (charing): IR 3475, 3350, 3255 (NH); 2220 (C ≡ N), 1655 (NH_2) and 1540 (C=N). Calc for $C_{18}H_{15}BrN_4O$: C, 56.39; H, 3.94; Br, 20.87; N, 14.63. Found: C, 56.5; H, 4.1; Br, 20.6; N, 14.5%.

4-Amino-5-cyano-2,6-diphenylpyrimidine **8a.**

8a.HBr (1 g) was dissolved in 30 ml dioxan and the soln was neutralized with Na_2CO_3aq. The ppt was dried and crystallised from dioxan in 90% yield, m.p. 202: IR 3450, 3345, 3255 (NH); 2220 (CN); 1650 (NH_2) and 1540 (C=N). Calc for $C_{17}H_{12}N_4$: C, 74.97; H, 4.44; N, 20.59. Found: C, 75.2; H, 4.5; N, 20.5%.

REFERENCES

[1]K. Suguira, A. F. Schmid, M. M. Schmid and F. G. Brown, *Cancer Chemother. Rep.* Part 2, **3**(1), 231 (1973).

[2]G. L. Regnier, R. J. Canevar, J. C. Le Douarec, S. Holstop and J. Daussy, *J. Med. Chem.* **15**, 295 (1972).

[3]G. N. Pershin, L. I. Sherbakova, T. N. Zykova and V. N. Sokolova, *Farmakol. Toksikol* **35**(4), 466 (1972); *Chem. Abstr.* **77**, 135580z (1972).

[4]G. Matolcsy, *World Rev. Pest Contr.* **10**, 50 (1971); *Chem. Abstr.* **76**, 82031s (1972).

[5]L. P. Prikazchikova, B. M. Khutova, I. F. Vladimirtsev, I. V. Boldyrev and N. I. Zhuravskaya, *Fiziol. Akt. Veshchestva* **7**, 84 (1975); *Chem Abstr* **83**, 127346m (1975).

[6]F. Kunckell and R. Bauer, *Ber. Dtsch. Chem. Ges.* **34**, 3030 (1901).

[7]J. Evans and T. B. Johnsons, *J. Am. Chem. Soc.* **52**, 4993 (1930).

[8]D. T. Brown, E. Hoerger and S. F. Mason, *J. Chem. Soc.* 211 (1955).

[9]K. Tokuyama, *Japan Kokai* **74** 69, 679; *Chem. Abstr.* 81, 13177t (1974).

[10]L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, p. 359, Pergamon Press, London (1969).