Synthesis of 5,7-diarylpyrido[2,3-*d*]pyrimidine derivatives catalysed by KF-alumina

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A series of 5,7-diarylpyrido[2,3-*d*]pyrimidine derivatives were synthesised by the reaction of 1,3-diaryl-2-propen-1-ones with 6-aminouracil in ethanol at 80°C catalysed by KF-Al_2O_3. The structure of one of the products was confirmed by X-ray analysis.

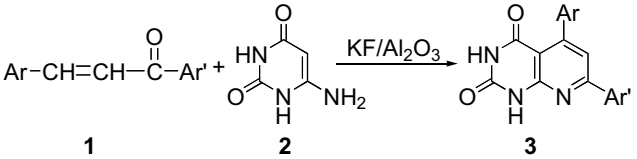
Keywords: fused pyridines, pyrimidines, KF-Al_2O_3, 6-aminouracil

Pyridopyrimidines and their derivatives are of great interest in organic chemistry, because it has been reported that they possess biological and pharmacological properties, such as antifolate,[1] antibacterial,[2] tyrosine kinase,[3] antimicrobial,[4] calcium channel antagonist,[5] anti-inflammatory and analgesic,[6] antileishmanial,[7] tuberculostatic,[8] anticonvulsant,[9] diuretic and potassium-sparing,[10] and antiaggressive[11] activities. This prompted us to investigate the synthesis of these compounds through a simple route. The utility of fluoride salts as potential base in a variety of synthetic reactions has been recognised in recent years.[12] In particular, potassium fluoride coated on alumina (KF-alumina) has been a versatile solid-supported reagent developed by Ando *et al*. for alkylation.[13] Over the years, the reagent has found application in a large number of organic reactions, such as the Knoevenagel,[14] Henry,[15] Darzens[16] and Wittig[17] reactions, eliminations,[16] and many other reactions.[18] In previous papers,[19,20] we have reported the synthesis of pyrido[2,3-*d*]pyrimidine from aldehyde, malononitrile or cyanoacetate with 6-aminouracil, using this reagent. Herein we report an efficient synthesis of 5,7-diarylpyrido[2,3-*d*]pyrimidine derivatives by the reaction of 1,3-diaryl-2-propen-1-ones and 6-aminouracil catalysed by KF–Al_2O_3.

When the 1,3-diaryl-2-propen-1-one (**1**), and 6-aminouracil (**2**) were treated with KF-Al_2O_3 in ethanol at 80°C, the desired 5,7-diarylpyrido[2,3-*d*]pyrimidine derivatives (**3**) were obtained (Scheme 1) in high yields, which were the products of further aromatisation.

In order to demonstrate the efficiency and scope of the present method, we applied the reaction of a variety of 1,3-diaryl-2-propen-1-ones with 6-aminouracil in the presence of KF–Al_2O_3 at 80°C in EtOH. As shown in Table 1, the reaction proceeded smoothly to afford the corresponding products **3** in good yields. All the products were characterised by ^{1}H NMR, IR spectra and elemental analysis. The structure of **3a** was further confirmed by X-ray analysis.[21] the structure of **3a** was shown in Fig. 1.

To form the structure **3**, a sequence of Michael addition, intramolecular condensation, followed by aromatisation may take place. It has been reported[22] that dihydropyrido[2,3-*d*]



1 **2** **3**

Scheme 1

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Table 1 The synthetic data of the products **3**

Entry	Ar	Ar'	Time/h	M.p./°C	Yields/%
3a	C_6H_5	4-ClC_6H_4	6	288-289	87
3b	C_6H_5	C_6H_5	8	272-274	93
3c	4-$CH_3C_6H_4$	4-ClC_6H_4	6	>300	87
3d	C_6H_5	3-ClC_6H_4	6	260-262	89
3e	3,4-$(CH_3O)_2C_6H_3$	C_6H_5	10	284-286	86
3f	C_6H_5	4-BrC_6H_4	10	>300	91
3g	4-ClC_6H_4	C_6H_5	8	>300	83
3h	4-$CH_3C_6H_4$	C_6H_5	8	285-286	83
3i	2,4-$Cl_2C_6H_3$	C_6H_5	5	>300	88
3j	4-BrC_6H_4	3-ClC_6H_4	5	>300	98

pyrimidine derivatives are unstable to air oxidation, giving their corresponding aromatisation products. We tried to obtain intermediates by carrying out the reactions under dry nitrogen, but the same products were obtained. A possible route to **3** is shown in Scheme 2.

In conclusion: we have found a convenient method for the synthesis of 5,7-diarylpyrido[2,3-*d*]pyrimidine derivatives by the reaction of 1,3-diaryl-2-propen-1-ones with 6-aminouracil catalysed by KF-Al_2O_3. This method has the advantage of easy work-up, mild reaction conditions and good yields the in synthesis of these potential biologically active compounds.

Experimental

Melting points were determined in open capillaries. IR spectra were recorded on a Tensor 27 spectrometer of samples in KBr. ^{1}H NMR spectra were measured in DMSO-d_6 on a Bruker 400 spectrometer

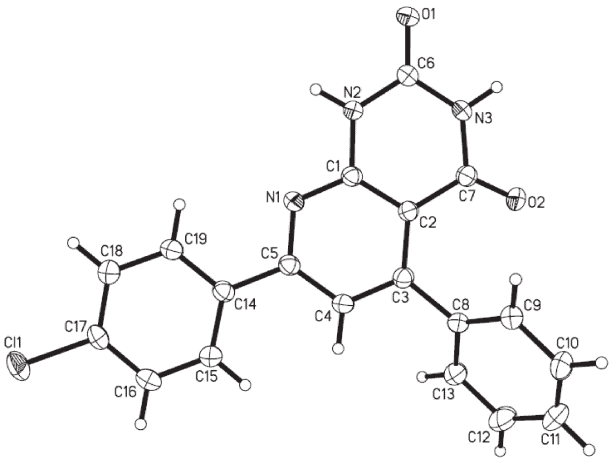
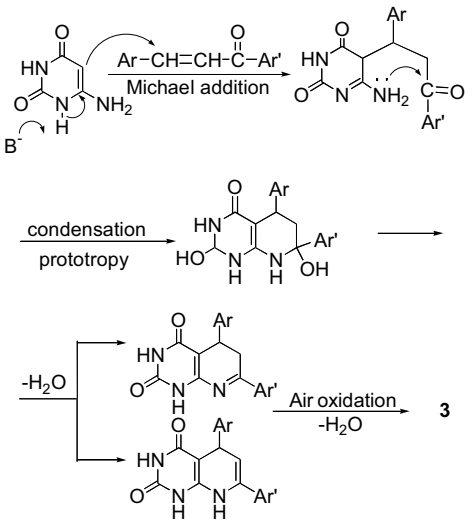


Fig. 1 The crystal structure of the product 3a (the DMF molecule of crystallisation has been omitted for clarity).



Scheme 2

using TMS an internal standard. Elemental analyses were carried out using a Carlo Erba 1110 analyser.

6-Aminouracil was purchased from Aldrich Chemical Company, Inc. The 1,3-diaryl-2-propen-1-ones were prepared as reported in reference 23.

General procedure for the synthesis of 5,7-diarylpyrido[2,3-d] pyrimidines **3**

A dry 100 ml flask was charged with 1,3-diaryl-2-propen-1-one **1** (4 mmol), 6-aminouracil **2** (4 mmol), KF/Al_2O_3 (500 mg) and EtOH (15 ml), The mixture was stirred at 80°C for 5–10 h. Then after being cooled to room temperature, the solid material was filtered off. The solid material was heated with sufficient DMF–H_2O to dissolve the product. The solid catalyst was filtered off and the product was allowed to crystallise. Solvent was removed by keeping the crystalline product at 100°C for 5 hours *in vacuo*, to give **3** as a pale yellow powder.

7-(4-Chlorophenyl)-5-phenyl compound (**3a**): M.p. 288–289°C. IR: ν_{max} 3174, 3061, 1712, 1690, 1587, 1553, 1490, 1399, 1263 cm^{-1}. ^1H NMR: δ 7.43 (s, 5H, ArH), 7.57 (s, 1H, ArH), 7.61 (d, *J* = 8.4 Hz, 2H, ArH), 8.25 (d, *J* = 8.4 Hz, 2H, ArH), 11.21 (s, 1H, NH), 11.83 p.p.m. (s, 1H, NH). Anal. Calcd for $C_{19}H_{12}ClN_3O_2$: C 65.24, H 3.46, N 12.01. Found C 65.09, H 3.52, N 12.28%.

5,7-Diphenyl compound (**3b**): M.p. 272–274°C. IR: ν_{max} 3469, 3057, 1716, 1701, 1595, 1547, 1493, 1442, 1407, 1367, 1237 cm^{-1}. ^1H NMR: δ 7.43–7.54 (m, 9H, ArH), 8.20–8.22(m, 2H, ArH), 11.32 (s, 1H, NH), 11.70 (s, 1H, NH). Anal. calcd for $C_{19}H_{13}N_3O_2$: C 72.37, H 4.16, N 13.33; found C 72.22, H 4.31, N 13.12.

7-(4-Chlorophenyl)-5-(4-tolyl) compound (**3c**): M.p. >300°C. IR: ν_{max} 3488, 3165, 3034, 2833, 1716, 1692, 1592, 1488, 1401, 1385, 1260 cm^{-1}. ^1H NMR: δ 2.51 (s, 3H, CH_3), 7.23 (d, *J* = 8.0 Hz, 2H, ArH), 7.34 (d, *J* = 8.4 Hz, 2H, ArH), 7.61 (d, *J* = 8.4 Hz, 2H, ArH), 8.25 (d, *J* = 8.4 Hz, 2H, ArH), 11.18 (s, 1H, NH), 11.76 (s, 1H, NH). Anal. calcd for $C_{20}H_{14}ClN_3O_2$: C 66.03, H 3.88, N 11.55; found C 66.09, H 3.90, N 11.81.

7-(3-Chlorophenyl)-5-phenyl compound (**3d**): M.p. 260–262°C. IR: ν_{max} 3498, 3180, 3061, 1723, 1594, 1521, 1495, 1401, 1260, 1242 cm^{-1}. ^1H NMR: δ 7.43 (s, 5H, ArH), 7.0–7.54 (m, 2H, ArH), 7.64 (s, 1H, ArH), 8.21 (d, *J* = 8.0 Hz, 2H, ArH), 8.21 (s, 1H, ArH), 11.22 (s, 1H, NH), 11.31 (s, 1H, NH). Anal. calcd for $C_{19}H_{12}ClN_3O_2$: C 65.24, H 3.46, N 12.01; found C 65.11, H 3.67, N 12.14.

5-(3,4-Dimethoxyphenyl)-7-phenyl compound (**3e**): M.p. 284–286°C. IR: ν_{max} 3576, 3487, 3029, 2838, 1721, 1695, 1596, 1582, 1519, 1445, 1401, 1368, 1260 cm^{-1}. ^1H NMR: δ 3.77 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 7.01–7.09 (m, 3H, ArH), 7.53–7.54 (m, 4H, ArH), 8.21–8.23 (m, 2H, ArH), 11.17 (s, 1H, NH), 11.64 (s, 1H, NH). Anal. calcd for $C_{21}H_{17}N_3O_4$: C 67.19, H 4.56, N 11.19; found C 67.06, H 4.58, N 11.35.

7-(4-Bromophenyl)-5-phenyl compound (**3f**): M.p. >300°C. IR: ν_{max} 3180, 3064, 1711, 1692, 1590, 1486, 1443, 1401, 1358, 1261 cm^{-1}. ^1H NMR: δ 7.43 (s, 5H, ArH), 7.56 (s, 1H, ArH), 7.74 (d, *J* = 8.4 Hz, 2H, ArH), 8.17 (d, *J* = 8.4 Hz, 2H, ArH), 11.20 (s, 1H, NH), 11.72 (s, 1H, NH). Anal. calcd for $C_{19}H_{12}BrN_3O_2$: C 57.89, H 3.07, N 10.66; found C 57.71, H 3.22, N 10.68.

5-(4-Chlorophenyl)-7-phenyl compound (**3g**): M.p. >300°C. IR: ν_{max} 3137, 3056, 1718, 1582, 1555, 1486, 1405, 1362, 1263 cm^{-1}. ^1H NMR: δ 7.47 (s, 4H, ArH), 7.52–7.55 (m, 4H, ArH), 8.21 (d, *J* = 8.4 Hz, 2H, ArH), 11.25 (s, 1H, NH), 11.73 (s, 1H, NH). Anal. calcd for $C_{19}H_{12}ClN_3O_2$: C 65.24, H 3.46, N 12.01; found C 65.20, H 3.51, N 12.10.

7-Phenyl-5-(4-tolyl) compound (**3h**): M.p. 285–286°C. IR: ν_{max} 3541, 3177, 3054, 2835, 1708, 1592, 1551, 1514, 1446, 1408, 1364, 1263 cm^{-1}. ^1H NMR: δ 2.51 (s, 3H, CH_3), 7.22 (d, *J* = 8.0 Hz, 2H, ArH), 7.34 (d, *J* = 8.0 Hz, 2H, ArH), 7.50–7.54 (m, 4H, ArH), 8.19–8.20 (m, 2H, ArH), 11.18 (s, 1H, NH), 11.67 (s, 1H, NH). Anal. calcd for $C_{20}H_{15}N_3O_2$: C 72.94, H 4.59, N 12.76; found C 72.88, H 4.81, N 12.59.

5-(2,4-Dichlorophenyl)-7-phenyl compound (**3i**): m.p. >300°C. IR: ν_{max} 3430, 3166, 3046, 1716, 1590, 1563, 1475, 1401, 1362, 1273, 1241 cm^{-1}. ^1H NMR: δ 7.41 (d, *J* = 8.0 Hz, 1H, ArH), 7.51–7.55 (m, 4H, ArH), 7.61 (s, 1H, ArH), 7.70 (s, 1H, ArH), 8.20–8.22 (m, 2H, ArH), 11.30 (s, 1H, NH), 11.83 (s, 1H, NH). Anal. calcd for $C_{19}H_{11}Cl_2N_3O_2$: C 59.39, H 2.89, N 10.94; found C 59.28, H 2.55, N 10.90.

5-(4-Bromophenyl)-7-(3-chlorophenyl) compound (**3j**): m.p. >300°C. IR: ν_{max} 3180, 3043, 1720, 1655, 1594, 1576, 1552, 1485, 1404, 1359, 1261 cm^{-1}. ^1H NMR: δ 7.40 (d, *J* = 8.0 Hz, 2H, ArH), 7.58–7.62 (m, 6H, ArH), 8.24 (d, *J* = 8.4 Hz, 2H, ArH), 11.24 (s, 1H, NH), 11.76 (s, 1H, NH). Anal. calcd for $C_{19}H_{11}BrClN_3O_2$: C 53.24, H 2.59, N 9.80; found C 53.11, H 2.68, N 9.90.

We are grateful to the Natural Science Foundation (04KJB150139) of the Education Committee of Jiangsu Province for financial support.

Received 25 September 2005; accepted 19 January 2006
Paper 05/3508

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21 X-ray crystallography for **3a**: Crystallographic data for the structure **3a** reported in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication with

No. CCDC-291527. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: + 44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Empirical formula $C_{19}H_{12}ClN_3O_2 \cdot HCON(CH_3)_2$, F_W = 422.86, T = 193(2) K, triclinic, space group P-1, a = 7.6985(7) Å, b = 11.7486(10) Å, c = 12.0533(8) Å, α = 72.813(7), β = 72.868(7), γ = 80.952(8) °, V = 992.34(14) Å^3, Z = 2, Dc = 1.415 Mg/m^3, λ (MoKα) = 0.71070Å, μ = 0.225 mm^{-1}, F(000) = 440, 3.03°<θ<25.35°, R = 0.0377, wR = 0.0904. S = 1.075, Largest diff. peak and hole: 0.234 and -0.252 e·Å^{-3}

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