



Research Article

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Synthesis of spiro pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidines using KF-alumina catalyst

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ABSTRACT

KF-alumina catalyzed condensation of 6-amino-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]-pyridine-5-carboxamide with cyclic ketone and aryl or alkyl ketones to provide spiro pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidine and pyrazolopyridopyrimidines derivatives respectively.

Keywords: Spiro pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidine, Pyrazolopyridopyrimidines, KF-alumina.

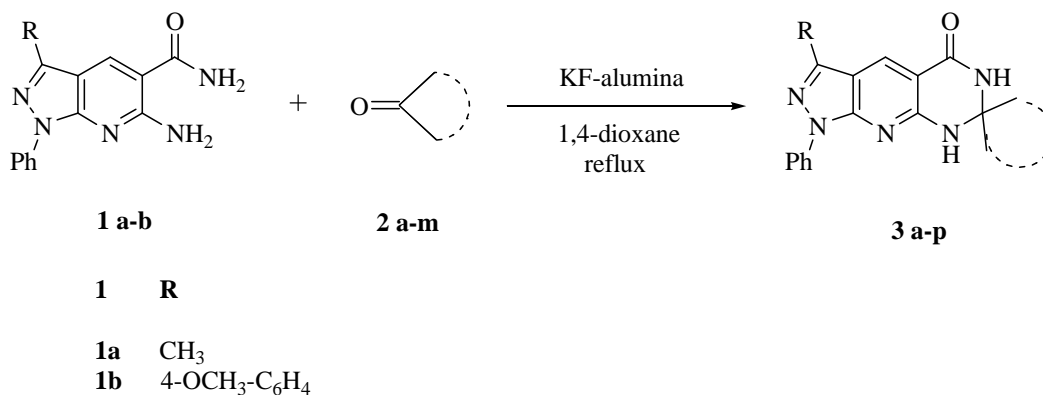
INTRODUCTION

Pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidines **3** have wide applications as colorants [1], heat/ moisture resistant and thermaltransfer printing agents [2], as well as photographic couplers [3]. They also display wide range of pharmacological activities such as anticonvulsants [4], anti-malarial agents [5], anti-inflammatories and central nervous system depressants [6]. Moreover, these types of compounds are inhibitors of cyclic guanosine-3',5'-monophosphate phosphodiesterase (*cGMP PDE*), and are thus agents against erectile dysfunction [7]. They also act as antiproliferative agents [8]. Our interest in this area encouraged us to explore the synthesis of new polysubstituted spiro pyrazolopyridopyrimidines. Organic reactions promoted by a solid heterogeneous catalyst have attracted widespread interest because of operational simplicity, high selectivity, and clean separation of products. Potassium fluoride impregnated over alumina (KF-alumina) is a remarkably useful green heterogeneous catalyst to promote a wide range of organic reactions [9-14]. Spiro cyclic systems containing one carbon atom common to two rings are structurally interesting [15-17]. Compound **1** has been synthesized by using reported method [18]. Herein we report simple efficient synthesis of spiro pyrazolopyridopyrimidines derivatives **3** by condensation of *o*-aminocarboxamide **1** with ketones (**2**) using KF-alumina catalyst (Scheme 1).

EXPERIMENTAL SECTION

Melting points were determined on a Barnstead Electro thermal melting point apparatus, Mod. No. IA-9200 in open capillary tubes and are uncorrected. The ¹H (400 MHz) and ¹³C (100 MHz) NMR spectra were measured in DMSO-*d*₆ on a Varian XL-400 spectrometer using tetramethylsilane as the internal standard. The IR spectra were recorded using a Shimadzu IR-408 instrument. Mass spectra (MS) were recorded on Shimadzu LCMS-2010A instrument. Elemental analyses were performed on a Hosli CH-Analyzer. All reactions were monitored by thin layer chromatography on 0.2 mm silica gel 60 F₂₅₄ (Merck) plates using UV light (254 and 366 nm) for detection. Column

chromatography was carried out on silica gel plates (SD Fine Chemicals, 60-120 mesh). Common reagent-grade chemicals are commercially available and were used without further purification.



Scheme 1 Synthesis of pyrazolopyridopyrimidines

General procedure for the synthesis of pyrazolopyridopyrimidine derivatives

To a mixture of *o*-aminocarboxamide **1** (2.0 g, 1 mol) in 1,4-dioxane (20 ml), the ketone **2** (1.2 mol) and KF-alumina (10 % mol) were added. The reaction mixture heated to reflux gently in oil bath indicated period time in (Table 2). The progress of the reaction was monitored by TLC using solvent system (ethyl acetate-hexane 50:50). After completion of the reaction, cooled the reaction mixture at room temperature and quenched in the water (100 ml) and extracted with ethyl acetate (2 X 25 ml). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give crude product, which was crystallized from ethanol.

6-amino-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide (1a)

Off-white solid, m. p. 195-196 °C, IR (KBr): 3300, 3150, 1668, 1618, 1476 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 2.47 (s, 3H), 7.20 (t, 1H, *J* = 5.2, 8 Hz), 7.38 (s, 1H), 7.45 (t, 2H, *J* = 5.64, 8.48 Hz), 7.76 (s, 2H), 8.05 (s, 1H), 8.26 (d, 2H, *J* = 8 Hz), 8.53 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 169.88, 159.3, 151.06, 144.08, 139.50, 132.33, 128.84 (2 C's), 124.65, 119.37 (2 C's), 108.79, 106.68, 12.06; ESIMS *m/z* 267.11 (M⁺). Anal. Calcd. for C₁₄H₁₃N₅O: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.62; H, 4.74; N, 26.37.

6-amino-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide (1b)

Off-white solid, m. p. 252-255 °C, IR (KBr): 3370, 3118, 1645, 1610, 1485 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 3.86 (s, 3H, OCH₃), 7.12 (d, 2H, *J* = 8.0 Hz), 7.29 (t, 1H, *J* = 8.0, 16.0 Hz), 7.49 (m, 3H), 7.84 (s, 1H, NH), 8.05 (d, 2H, *J* = 8.8 Hz), 8.36 (d, 3H, *J* = 7.6 Hz), 8.72 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 169.84, 159.80, 158.85, 151.54, 144.74, 139.35, 132.90, 128.90 (2 C's), 128.47 (2 C's), 125.19, 124.64, 120.10 (2 C's), 114.31 (2 C's), 107.89, 106.44, 55.24; ESIMS *m/z* 359.26 (M⁺). Anal. Calcd. for C₂₀H₁₇N₅O₂: C, 66.84; H, 4.77; N, 19.49. Found: C, 66.71; H, 4.70; N, 19.38.

3-methyl-1-phenyl-6,8-dihydrospiro[cyclopentane-1H-pyrazolo[4',3':5,6]pyrido[2,3-d]-pyrimidine]-5-one (3a)

Off-white solid, m. p. 282-283 °C, IR (KBr): 3317, 3125, 1631, 1604, 1490 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 1.69 (m, 4H), 1.86 (m, 4H), 2.48 (s, 3H, CH₃), 7.24 (m, 1H), 7.47 (m, 2H), 8.13 (s, 1H), 8.21 (d, 2H, *J* = 8.2 Hz), 8.41 (s, 1H), 8.49 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 163.14, 157.44, 152.18, 145.30, 139.51, 131.79, 129.46 (2 C), 125.74, 120.44 (2 C's), 110.95, 106.75, 77.01, 66.74 (2 C's), 22.62 (2 C's), 12.42; ESIMS *m/z* 333 (M⁺). Anal. Calcd. for C₁₉H₁₉N₅O: C, 68.45; H, 5.74; N, 21.01. Found: C, 68.74; H, 5.44; N, 21.16.

3-methyl-1-phenyl-2',3',6,8-tetrahydrospiro[inden-e-1H-pyrazolo[4',3':5,6]pyrido[2,3-d]-pyrimidin]-5-one (3b)

Pale yellow solid, m. p. 289-290 °C, IR (KBr): 3410, 3178, 1685, 1617, 1502 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 2.42 (m, 2H), 2.50 (s, 3H, CH₃), 2.99 (m, 2H), 7.14-7.22 (m, 5H), 7.44 (m, 2H), 8.21 (m, 2H), 8.50 (d, 2H, *J* = 7.8 Hz), 8.80 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 161.92, 156.32, 151.80, 146.03, 146.72, 144.72, 141.27, 139.25, 131.16, 128.84, 126.96, 125.18, 124.98 (2 C's), 121.73, 119.68 (2 C's), 110.62, 106.24, 77.96, 66.30, 27.71, 12.06; ESIMS *m/z* 381.16 (M⁺). Anal. Calcd. for C₂₃H₁₉N₅O: C, 72.42; H, 5.02; N, 18.36. Found: C, 72.78; H, 5.18; N, 18.36.

7'-methoxy-3-methyl-1-phenyl-3',4',6,8-tetrahydro-2H-spiro-[naphthalene-1H-pyrazolo- [4',3':5,6]pyrido[2,3-d]-pyrimidin]-5-one (3c)

Pale yellow solid, m. p. 202-203 °C, IR (KBr): 3330, 3162, 1647, 1620, 1470 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 1.87 (m, 2H), 1.89 (m, 2H), 2.50 (s, 3H, CH₃), 2.68 (m, 2H), 3.67 (s, 3H, OCH₃), 6.87 (d, 1H, *J* = 12.0 Hz), 7.07 (m, 2H), 7.21 (m, 1H), 7.43 (m, 2H), 8.26 (d, 2H, *J* = 8.0 Hz), 8.40 (s, 2H), 8.47 (s, 1H), 8.62 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 161.60, 157.49, 157.06, 151.97, 144.66, 140.21, 139.36, 131.09, 129.76, 129.11, 128.81, 124.84, 119.50, 114.65, 111.95, 110.49, 105.61, 68.85, 66.31, 55.09, 27.93, 18.02, 12.08; ESIMS *m/z* 425 (M⁺). Anal. Calcd. for C₂₅H₂₃N₅O: C, 70.57; H, 5.45; N, 16.46. Found: C, 70.30; H, 5.29; N, 16.68.

3-methyl-1-phenyl-6,8-dihydrospiro[cyclohex[2]ene-1H-pyrazolo[4',3':5,6]pyrido[2,3-d]-pyrimidin]-5-one (3d)

Off-white solid, m. p. 267-268 °C, IR (KBr): 3318, 3140, 1664, 1610, 1501 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 1.76 (m, 3H), 1.80 (m, 4H), 2.50 (s, 3H, CH₃), 5.72 (d, 2H, CH, *J* = 8.0 Hz), 5.81 (d, 2H, CH, *J* = 8.0 Hz), 7.24 (m, 1H), 7.46 (m, 2H), 8.05 (s, 1H), 8.25 (d, 2H, *J* = 8.0 Hz), 8.41 (d, 2H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 162.50, 157.06, 156.16, 150.19, 146.21, 140.26, 138.43, 133.18, 129.94, 129.02, 126.38, 123.22, 118.25, 113.06, 111.62, 110.32, 104.66, 68.50, 67.12, 56.83, 26.13, 18.15, 11.20; ESIMS *m/z* 345 (M⁺). Anal. Calcd. for C₂₀H₁₉N₅O: C, 69.55; H, 5.54; N, 20.28. Found: C, 69.64; H, 5.22; N, 20.31.

3-methyl-1-phenyl-6,8-dihydrospiro [3,3-dimethyl-1,5-dioxaspiro[5.5] undecane]-1H-pyrazolo- [4',3':5,6]pyrido [2,3-d]-pyrimidine]-5-one (3e)

Off-white solid, m. p. 262-263 °C, IR (KBr): 3352, 3128, 1664, 1635, 1455 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 0.89 (s, 6H), 1.80 (m, 8H), 2.50 (s, 3H), 3.44 (s, 4H), 7.25 (m, 1H), 7.47 (m, 2H), 8.07 (s, 1H), 8.27 (m, 2H), 8.41 (s, 1H), 8.46 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 162.47, 156.68, 151.87, 144.57, 139.35, 131.16, 128.86, 124.92, 119.63, 110.58, 106.51, 96.10, 68.99, 67.55, 34.18, 29.75, 26.97, 22.26, 12.04; ESIMS *m/z* 447 (M⁺). Anal. Calcd. for C₂₆H₃₃N₅O₃: C, 67.10; H, 6.53; N, 15.65. Found: C, 67.32; H, 6.52; N, 15.45.

3',3',3,5'-tetramethyl-1-phenyl-6,8-dihydrospiro[cyclohexane-1H-pyrazolo[4',3':5,6]pyrido-[2,3-d] pyrimidin]-5-one (3f)

Off-white solid, m. p. 273-274 °C, IR (KBr): 3352, 3170, 1661, 1630, 1503 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 0.88 (s, 3H), 0.90 (m, 2H), 0.98 (m, 6H), 1.82 (d, 2H), 1.84 (m, 2H), 2.24 (m, 1H), 2.52 (s, 3H), 7.24 (m, 1H), 7.48 (m, 2H), 7.76 (s, 1H), 8.23 (s, 1H), 8.28 (d, 2H), 8.45 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 163.13, 155.90, 151.96, 144.60, 139.40, 131.04, 128.90, 124.93, 119.69, 110.59, 107.05, 68.55, 49.92, 46.82, 44.55, 33.70, 31.21, 26.00, 23.35, 22.11, 12.04; ESIMS *m/z* 389.22 (M⁺). Anal. Calcd. for C₂₃H₂₇N₅O: C, 70.93; H, 6.99; N, 17.98. Found: C, 70.67; H, 6.63; N, 17.72.

3-methyl-1-phenyl-6,8-dihydrospiro[cyclohexane-1H-pyrazolo[4',3':5,6]pyrido[2,3-d]-pyrimidin]-5-one (3g)

Off-white solid, m. p. 286-287 °C, IR (KBr): 3308, 3160, 1655, 1608, 1503 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 1.23 (m, 1H), 1.29 (m, 1H), 1.40 (m, 4H), 1.62 (m, 4H), 2.50 (s, 3H), 7.26 (s, 1H), 7.48 (m, 2H, *J* = 8.0 Hz), 7.95 (s, 1H), 8.25 (dd, 2H, *J* = 8.0 Hz), 8.41 (d, 1H, *J* = 8.2 Hz); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 163.36, 157.22, 152.43, 145.58, 139.58, 131.99, 129.68, 126.02, 120.71, 111.12, 106.80, 68.46, 66.89, 24.79, 21.29, 12.54; ESIMS *m/z* 347 (M⁺). Anal. Calcd. for C₂₀H₂₁N₅O: C, 69.14; H, 6.09; N, 20.16. Found: C, 69.01; H, 6.12; N, 20.05.

3,7-dimethyl-1,7-diphenyl-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]-pyrimidin-5-one (3h)

Off-white solid, m. p. 254-255 °C, IR (KBr): 3438, 3172, 1646, 1612, 1500 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 1.75 (m, 3H), 2.44 (s, 3H), 7.19 (m, 4H), 7.30 (m, 4H), 8.21 (d, 2H, *J* = 8 Hz), 8.36 (s, 1H), 8.92 (s, 1H), 9.14 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 163.07, 156.65, 151.63, 147.47, 144.68, 139.18, 131.40, 128.84 (2 C's), 128.13 (2 C's), 125.12, 124.88, 119.78 (2 C's), 110.65, 106.92, 69.79, 30.02, 11.97; ESIMS *m/z* 369.16 (M⁺). Anal. Calcd. for C₂₂H₁₉N₅O: C, 71.53; H, 5.18; N, 18.96. Found: C, 71.81; H, 5.34; N, 18.73.

7-(2-methoxyphenyl)-3,7-dimethyl-1-phenyl-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido- [2,3-d]pyrimidin-5-one (3i)

Pale yellow solid, m. p. 232-236 °C, IR (KBr): 3455, 3185, 1650, 1608, 1504 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 1.86 (s, 3H), 2.47 (s, 3H), 3.88 (s, 3H), 6.82 (s, 1H), 7.02 (s, 1H), 7.21 (m, 3H), 7.51 (t, 2H, *J* = 7.6, 8 Hz), 8.25 (d, 2H, *J* = 8.4 Hz), 8.37 (s, 1H), 8.40 (s, 1H), 8.63 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 163.14, 157.45, 156.84, 152.13, 145.22, 139.74, 134.02, 131.84, 129.74, 129.47 (2 C's), 126.40, 125.62, 120.34 (2

C's), 116.5, 112.92, 113.32, 107.16, 70.29, 56.07, 27.85, 12.20; ESIMS m/z 399.17 (M⁺). Anal. Calcd. for C₂₃H₂₁N₅O₂: C, 69.16; H, 5.30; N, 17.53. Found: C, 69.42; H, 5.60; N, 17.28.

7-(3-methoxyphenyl)-3,7-dimethyl-1-phenyl-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido-[2,3-d]-pyrimidin-5-one (3j)

Pale yellow solid, m. p. 245-246 °C, IR (KBr): 3490, 3170, 1665, 1601, 1502 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 1.85 (s, 3H), 2.45 (s, 3H), 3.86 (s, 3H), 6.81 (s, 1H), 7.00 (s, 1H), 7.19 (m, 3H), 7.49 (t, 2H, *J* = 7.2, 4.2 Hz), 8.23 (d, 2H *J* = 8.4 Hz), 8.35 (d, 1H, *J* = 8.4 Hz), 8.58 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 162.61, 156.92, 156.31, 151.61, 144.68, 139.22, 133.50, 131.29, 129.20, 128.92 (2 C's), 125.88, 125.08, 119.82 (2 C's), 116.06, 112.42, 111.80, 106.63, 69.78, 55.56, 27.58, 11.97; ESIMS m/z 399.25 (M⁺). Anal. Calcd. for C₂₃H₂₁N₅O₂: C, 69.16; H, 5.30; N, 17.53. Found: C, 69.37; H, 5.15; N, 17.92.

7-(4-methoxyphenyl)-3,7-dimethyl-1-phenyl-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido-[2,3-d]-pyrimidin-5-one (3k)

Pale yellow solid, m. p. 248-249 °C, IR (KBr): 3468, 3160, 1656, 1615, 1500 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 1.71 (s, 3H), 2.06 (s, 3H), 3.63 (s, 3H), 6.83 (d, 1H, *J* = 8 Hz), 7.25 (t, 1H), 7.41 (d, 2H, *J* = 8 Hz), 7.48 (t, 2H, *J* = 4.4, 7.2 Hz), 8.21 (d, *J* = 8 Hz 1H), 8.34 (s, 1H), 8.80 (s, 1H), 9.02 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 163.96, 157.46, 150.63, 149.80, 142.78, 136.25, 134.16, 130.68, 130.15 (2 C's), 128.11 (2 C's), 125.30, 118.03, 115.86 (2 C's), 112.85, 103.73, 67.34, 55.60, 23.88, 11.21; ESIMS m/z 399.25 (M⁺). Anal. Calcd. for C₂₃H₂₁N₅O₂: C, 69.16; H, 5.30; N, 17.53. Found: C, 69.06; H, 5.49; N, 17.31.

7-ethyl-3,7-dimethyl-1-phenyl-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]-pyrimidin-5-one (3l)

Pale yellow solid, m. p. 273-274 °C, IR (KBr): 3273, 3165, 1654, 1606, 1502 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 0.85 (m, 3H), 1.43 (s, 3H), 1.65 (m, 2H), 2.47 (s, 3H), 7.23 (t, 1H), 7.46 (t, 2H, *J* = 6.5, 8 Hz), 7.94 (s, 1H), 8.21 (t, 3H, *J* = 4.1, 8 Hz), 8.37 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 162.15, 156.91, 151.94, 144.55, 139.30, 130.89, 128.85 (2 C's), 124.95, 119.80 (2 C's), 110.18, 105.77, 69.33, 34.98, 29.01, 12.02, 7.99; ESIMS m/z 321.16 (M⁺). Anal. Calcd. for C₁₈H₁₉N₅O: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.11; H, 5.65; N, 21.94.

7,7-diethyl-3-methyl-1-phenyl-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido[2,3-d]-pyrimidin-5-one (3m)

Pale yellow solid, m. p. 276-277 °C, IR (KBr): 3270, 3160, 1648, 1610, 1502 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 0.84 (t, 6H), 1.61 (m, 4H), 2.46 (s, 3H), 7.23 (t, 1H, *J* = 5, 8 Hz), 7.46 (t, 2H), 7.82 (s, 1H), 8.08 (s, 1H), 8.21 (d, 2H), 8.33 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 162.80, 157.11, 150.98, 150.50, 144.50, 138.80, 131.12, 129.11 (2 C's), 123.65, 119.0 (2 C's), 112.14, 106.66, 66.89, 31.46 (2 C's), 7.95 (2 C's); ESIMS m/z 335.15 (M⁺). Anal. Calcd. for C₁₉H₂₁N₅O: C, 68.04; H, 6.31; N, 20.88. Found: C, 68.37; H, 6.14; N, 20.56.

3-(4-methoxyphenyl)-1-phenyl-6,8-dihydrospiro[cyclopentane-1H-pyrazolo[4',3':5,6]pyrido-[2,3-d]pyrimidine]-5-one (3n)

Off-white solid, m. p. 315-317 °C, IR (KBr): 3335, 3163, 1636, 1602, 1496 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 1.74 (m, 4H), 1.94 (m, 4H), 3.86 (s, 3H, OCH₃), 7.14 (d, 2H, *J* = 6.8 Hz), 7.32 (t, 1H, *J* = 8, 16 Hz), 7.54 (m, 2H), 7.96 (t, 2H, *J* = 4, 8 Hz), 8.29 (m, 1H), 8.61 (s, 1H), 8.64 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 162.24, 159.87, 156.76, 152.34, 145.00, 139.14, 131.63, 128.94 (2 C's), 128.26 (2 C's), 125.59, 124.48, 120.63 (2 C's), 114.53 (2 C's), 108.18, 107.44, 76.71, 55.24, 40.41 (2 C's), 22.19 (2 C's); ESIMS m/z 425.34 (M⁺). Anal. Calcd. for C₂₅H₂₃N₅O₂: C, 70.57; H, 5.45; N, 16.46. Found: C, 70.46; H, 5.22; N, 16.31.

3-(4-methoxy phenyl)-1-phenyl-6,8-dihydrospiro[cyclohexane-1H-pyrazolo[4',3':5,6]pyrido-[2,3-d]pyrimidin]-5-one (3o)

Off-white solid, m. p. 325-327 °C, IR (KBr): 3306, 3154, 1671, 1606, 1522 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 1.28 (m, 1H), 1.40 (m, 1H), 1.64 (m, 4H), 1.77 (m, 4H), 3.86 (s, 3H, OCH₃), 7.14 (d, 2H, *J* = 12 Hz), 7.32 (t, 1H, *J* = 8, 16 Hz), 7.54 (t, 2H, *J* = 8, 16 Hz), 7.96 (d, 2H, *J* = 8 Hz), 8.09 (s, 1H), 8.32 (d, 2H, *J* = 8 Hz), 8.53 (s, 1H), 8.60 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 162.18, 159.87, 156.40, 152.47, 144.98, 139.16, 131.49, 128.96 (2 C's), 128.26 (2 C's), 125.58, 124.49, 120.63 (2 C's), 114.54 (2 C's), 108.19, 107.39, 67.96, 55.24, 38.26 (2 C's), 24.41, 20.60 (2 C's); ESIMS m/z 438.82 (M⁺). Anal. Calcd. for C₂₇H₂₆N₄O₂: C, 73.95; H, 5.98; N, 12.78. Found: C, 73.76; H, 5.83; N, 12.56.

3-(4-methoxyphenyl)-7-methyl-1,7-diphenyl-1,6,7,8-tetrahydro-5H-pyrazolo[4',3':5,6]pyrido-[2,3-d]pyrimidin-5-one (3p)

Off-white solid, m. p. 298-300 °C, IR (KBr): 3341, 3164, 1651, 1629, 1482 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) (δ, ppm): 1.79 (s, 1H, CH₃), 3.84 (s, 3H, OCH₃), 7.09 (d, 2H, *J* = 8 Hz), 7.23 (m, 1H), 7.31 (m, 3H), 7.54 (m, 4H), 7.92 (d, 2H, *J* = 8 Hz), 8.30 (d, 2H, *J* = 16 Hz), 8.55 (s, 1H), 9.05 (s, 1H), 9.26 (s, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) (δ, ppm): 160.39, 157.20, 152.69, 147.98, 139.55, 132.29, 129.51, 128.82, 128.74 (2 C's), 128.32 (2 C's), 127.86, 126.9, 126.24, 125.40 (2 C's), 124.80, 121.21 (2 C's), 115.10(2 C's), 108.89, 108.30, 70.35 (2 C's), 55.73, 30.68; ESIMS *m/z* 461.28 (M⁺). Anal. Calcd. for C₂₈H₂₃N₅O₂: C, 72.87; H, 5.02; N, 15.17. Found: C, 72.74; H, 5.16; N, 15.09.

RESULTS AND DISCUSSION

o-Aminocarboxamide **1a** and cyclopentanone (**2a**) were chosen as model substrates to determine suitable reaction conditions. Several solvents and catalysts were examined to setup standard reaction conditions. The results of studies are summarized in (Table 1).

Table 1 Optimization of reaction condition

Entry	Catalyst (% mol)	Solvent	Yield ^a (%) 3a
1	KF-alumina (10)	EDC	37
2	KF-alumina (10)	DMF	43
3	KF-alumina (10)	1,4-dioxane	88
4	alumina basic (10)	1,4-dioxane	30
5	alumina neutral (10)	1,4-dioxane	46
6	Silica (10)	1,4-dioxane	no reaction
7	Alum (10)	1,4-dioxane	no reaction
8	ZnCl ₂ (10)	1,4-dioxane	70
9	BF ₃ -etherate (10)	1,4-dioxane	69
10	KF-alumina (5)	1,4-dioxane	56
11	KF-alumina (10)	^b	54

(a) Yield is based on **1**. (b) ⁻ reaction carried out without solvent.

As reported from (Table 1) several different catalyst was employed to carried condensation reaction such as KF-alumina, basic alumina, neutral alumina, silica, alum, ZnCl₂ and BF₃-etherate (Table 1, entries 1-11). Among the all catalysts 10 % KF-alumina found to be effective for this conversion. The yield of product increased in 1,4-dioxane (Table 1, entry 3). However, the yield was decreased when solvent was 1,2-Dichloroethane (EDC) and DMF (Table 1, entries 1 and 2). Moreover, we found that the yields of product were decreased when reaction was carried out without solvent (Table 1, entry 11). The loading of catalyst were optimized, 10 % mole KF-alumina gave higher yield (Table 1, entry 3). Lowering catalyst loading yield was dropped (Table 1, entry 10).

Table 2 Synthetic Results of 3a-p in 1,4-dioxane^a

Entry	R	Ketone (2)	Time (h)	Product	Yield ^b (%)
1	CH ₃	Cyclopentanone	3	3a	88
2	CH ₃	Indanone	8	3b	82
3	CH ₃	7-Methoxy-tetralone	7	3c	80
4	CH ₃	2-Cyclohexen-1-one	4	3d	84
5	CH ₃	3,3-Dimethyl-1,5-dioxaspiro[5.5]undecan-9-one	8	3e	78
6	CH ₃	3,3,5-Trimethyl cyclohexanone	4	3f	86
7	CH ₃	Cyclohexanone	3	3g	92
8	CH ₃	Acetophenone	4	3h	90
9	CH ₃	2-Methoxy acetophenone	5	3i	92
10	CH ₃	3-Methoxy acetophenone	5	3j	88
11	CH ₃	4-Methoxy acetophenone	5	3k	94
12	CH ₃	Methyl ethyl ketone	3	3l	86
13	CH ₃	3-Pentanone	4	3m	82
14	p-CH ₃ O-C ₆ H ₄	Cyclopentanone	3	3n	90
15	p-CH ₃ O-C ₆ H ₄	Cyclohexanone	4	3o	88
16	p-CH ₃ O-C ₆ H ₄	Acetophenone	4	3p	92

^a Reaction condition: KF-alumina (10 % mol), **1** (1 mol), **2** (1.2 mol), Reflux temp. ^b Isolated yields is based on **1**.

Under optimized reaction conditions (Table 1, entry 3) wide range of ketones was utilized to study scope of reaction the results of study are summarized in (Table 2).

CONCLUSION

In summary, a mild, facile and environmentally benign method has been developed for the synthesis of pyrazolopyridopyrimidine derivatives in high yields catalyzed by KF-alumina. The advantages of this procedure include its mild reaction conditions, high yields, one-pot method operational simplicity and environmental benignity.

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