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A facile, KF/Al_2O_3 mediated method for the preparation of functionalized pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones

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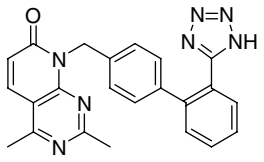
Abstract—A series of functionalized pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones were prepared by a KF/Al_2O_3 mediated condensation of 4-(alkylamino)-2-(methylthio)pyrimidine-5-carbaldehydes and phenyl acetic acid ester derivatives.

Over the past several decades, two of the major trends in the field of organic chemistry have been the push toward environmentally friendly processes and the development of directed libraries.[1] Both of these movements have had a dramatic impact on the practical application of synthetic chemistry, especially in the pharmaceutical industry. The drive for more environmentally friendly procedures, the need for increased efficiency, and the development of libraries of thousands of new chemical entities has led to an explosive growth in the fields of both solid phase organic synthesis and solid supported reagents such as potassium fluoride on alumina (KF/Al_2O_3). This versatile reagent was originally introduced in 1979 by Ando et al. as a useful agent for inducing alkylation reactions.[2] It possesses a number of advantages of both solution and solid phase chemistry. Like solid phase synthesis, excess support bound reagent can be used and removed by filtration, avoiding cumbersome aqueous work-ups and decreasing solvent waste handling issues. In addition, since the compound of interest is never covalently bound to the solid support, monitoring of the reactions and analysis can be accomplished using standard methods (thin layer chromatography, solution ^1H NMR, etc.). Also, the products are isolated by filtration and removal of the solvents, eliminating the need for a cleavage step that is required



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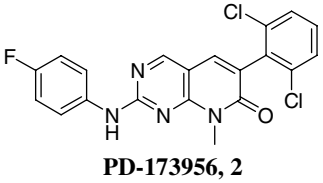

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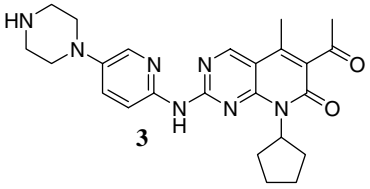

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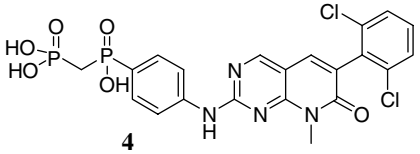

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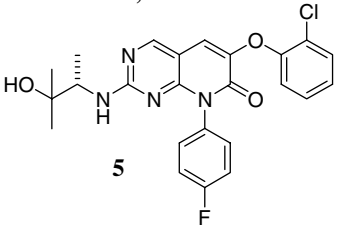

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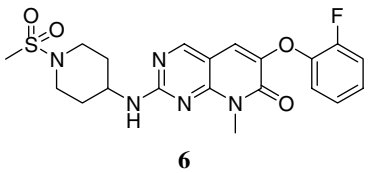

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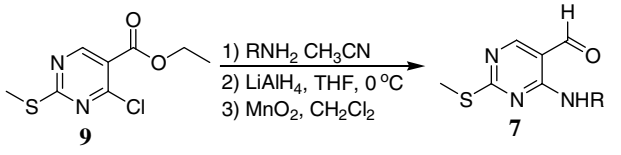
in solid phase preparations. Additional benefits have been achieved by taking advantage of the strongly basic nature of KF/Al_2O_3, which has allowed it to replace organic bases in a number of reactions including but not limited to selective N-alkylation of amides,[3] epoxidations,[4] diazetizations,[5] Sonogashira couplings,[6] Suzuki couplings,[7] Knoevenagel reactions,[8] and Horner–Emmons chemistry.[9]

As part of our continuing effort to explore the utility of KF/Al_2O_3, we recently examined it's utility in the synthesis of pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones and related compounds. This scaffold has been found in a variety of interesting compounds, including the angitonesin-2-antagonist tasosartan[10] (**1**) and tyrosine kinase inhibitors such as PD-173956 (**2**).[11] Further, a wide range of biological activity has been observed in compounds of this class, including CDK4 inhibition (**3**),[12] Src and Abl tyrosine kinase inhibition (**4**),[13] P38 MAP kinase inhibition (**5**, **6**),[14] hepatitis C polymerase inhibition,[15] PDE V inhibition,[16] telomerase inhibition,[17] and serine/threonine kinase inhibition.[18]

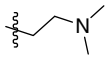
One of the primary methods to prepare the requisite pyrimidinone scaffold core for this class of compounds is a tandem Knovenagal and amide/ester exchange reaction between the functionalized pyrimidine aldehyde **7** and a suitable phenyl acetic acid derivative (**8**). When these reactions are performed using standard bases, such as K_2CO_3, the yield and purity of the crude products is moderate at best and extended reaction times are required.[19] We have recently found, however, that the application of KF/Al_2O_3 leads to a substantial improvement in the overall yield and purity of the desired final products, and significantly shorter reaction times.

The initial pyrimidine aldehydes are prepared from the commercially available pyrimidine ester **9** using a three step process. Nucleophilic displacement of the 4-Cl substituent with the desired primary amine is followed by sequential lithium aluminium hydride reduction. Subsequent manganese dioxide oxidation provides the necessary aminopyrimidine aldehydes, **7**.

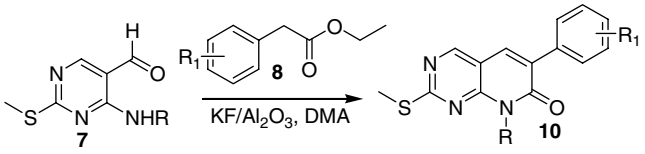


Cyclization of **7** to the final product in the presence of KF/Al_2O_3 was then attempted in a range of solvents including 1,4-dioxane, methylene chloride, THF, acetonitrile, 1,2-dichloroethane, and dimethyl acetamide. Surprisingly, only the reactions run in dimethyl acetamide provided the desired products at room temperature. In all of the other solvents, both at ambient and elevated temperatures, either no reaction occurred, or the results were complex mixtures of products. In the case of dimethylacetamide, however, nearly quantitative conversion to the 6,6-fused ring system **10** was observed at room temperature. The majority of the reactions examined were complete in less than 10 min. When the steric demands of the reagents were increased (e.g., entries 25 and 31), however, longer reaction time, heating, or both were required in order to produce the desired products (see Table 1).

Table 1. Representative examples of the synthesis of pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **10**[20]

Entry	R	R_1	Yield (%)
1	Me	H	85
2	Me	2-Me	81
3	Me	4-OH	75
4	Me	4-OMe	77
5	Me	2,5-Di-OMe	64
6	Me	4-*t*-Bu	85
7	Me	2,6-Di-Cl	87
8	Et	2-Me	83
9	Et	4-OH	87
10	Et	4-OMe	56
11	Et	2,5-Di-OMe	59
12	Et	4-*t*-Bu	87
13	Et	2,6-Di-Cl	60
14	Cyc-prop	2-Me	50
15	Cyc-prop	4-OH	37
16	Cyc-prop	4-OMe	59
17	Cyc-prop	2,5-Di-OMe	67
18	Cyc-prop	4-*t*-Bu	59
19	Cyc-prop	2,6-Di-Cl	Trace
20	Ph	2-Me	59
21	Ph	4-OH	60
22	Ph	4-OMe	73
23	Ph	2,5-Di-OMe	59
24	Ph	4-*t*-Bu	56
25	Ph	2,6-Di-Cl	41[a]
26	Bn	2-Me	68
27	Bn	4-OH	51
28	Bn	4-OMe	63
29	Bn	2,5-Di-OMe	49
30	Bn	4-*t*-Bu	64
31	Bn	2,6-Di-Cl	45[b]
32		2,6-Di-Cl	35

[a] Heated to 60 °C for 2 days.
[b] Stirred at rt for 4 days.



In summary, an efficient synthesis of a series of pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (**10**) from easily accessible starting materials was developed using the solid phase reagent, KF/Al_2O_3.

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20. Representative procedure: 4-amino-2-(methylthio) pyrimidine-5-carbaldehyde (100 mg, 0.55 mmol) and ethyl 2-phenylacetate (89 mg, 86.9 μL, 0.55 mmol) are dissolved in 5.0 mL DMA, 634 mg of KF/Al_2O_3 (40 wt %, KF, Sigma–Aldrich catalog #316385) is added, and the reaction is stirred for 15 min. The reaction is then filtered, the residual solid is washed with 15 mL CH_2Cl_2, and the combined organic solvents are stripped to a solid. Purification by flash chromatography with 3/1 hexane/EtOAc on silica gel provided 131 mg (85%) of the desired product, 8-methyl-2-(methylthio)-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one. Data from Table 1. Entry 1: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (s, 1H), 7.65 (s, 1H), 7.6 (d, 2H, $J = 6.3$ Hz), 7.37 (m, 3H), 3.76 (s, 3H), 2.59 (s, 3H); ($M+H^+$) 284. Entry 2: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H), 7.58 (s, 1H), 7.27 (m, 4H), 3.82 (s, 3H), 2.68 (s, 3H), 2.23 (s, 3H); ($M+H^+$) 298. Entry 3: ^{1}H NMR (300 MHz, CD_3OD): δ 8.20 (s, 1H), 7.95 (s, 1H), 7.58 (d, 2H, $J = 7.6$ Hz), 6.88 (d, 2H, $J = 7.8$ Hz), 3.83 (s, 3H), 2.70 (s, 3H); ($M+H^+$) 300. Entry 4: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H), 7.69 (s, 1H), 7.68 (d, 2H, $J = 8.7$ Hz), 6.97 (d, 2H, $J = 8.6$ Hz), 3.86 (s, 3H), 3.80 (s, 3H), 2.62 (s, 3H); ($M+H^+$) 314. Entry 5: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.69 (s, 1H), 6.94 (m, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 2.69 (s, 3H); ($M+H^+$) 344. Entry 6: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H), 7.67 (s, 1H), 7.61 (d, 2H, $J = 8.4$ Hz), 7.43 (d, 2H, $J = 8.3$ Hz), 3.80 (s, 3H), 2.63 (s, 3H), 1.33 (s, 9H); ($M+H^+$) 340. Entry 7: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.63 (s, 1H), 7.44 (d, 2H, $J = 7.1$ Hz), 7.31 (d, 1H, $J = 6.8$ Hz), 3.81 (s, 3H), 2.69 (s, 3H); ($M+H^+$) 352. Entry 8: ^{1}H NMR ($CDCl_3$): δ 8.63 (s, 1H), 7.56 (s, 1H), 7.27 (m, 4H), 4.56 (q, 2H, $J = 7.0$ Hz), 2.67 (s, 3H), 2.24 (s, 3H), 1.38 (t, 3H, $J = 7.0$ Hz); ($M+H^+$) 312. Entry 9: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.70 (s, 1H), 7.50 (d, 2H, $J = 8.7$ Hz), 6.85 (d, 2H, $J = 9.5$ Hz), 4.51 (q, 2H, $J = 7.1$ Hz), 2.58 (s, 3H), 1.53 (br s, 1H), 1.28 (t, 3H, $J = 7.1$ Hz); ($M+H^+$) 314. Entry 10: ^{1}H NMR ($CDCl_3$): δ 8.96 (s, 1H), 7.67 (s, 1H), 7.65 (d, 2H, $J = 8.8$ Hz), 6.99 (d, 2H, $J = 8.8$ Hz), 4.57 (q, 2H, $J = 7.0$ Hz), 3.87 (s, 3H), 2.67 (s, 3H), 1.39 (t, 3H, $J = 7.0$ Hz); (M+H) 328. Entry 11: ^{1}H NMR ($CDCl_3$): δ 8.49 (s, 1H), 7.60 (s, 1H), 6.95 (m, 3H), 4.42 (q, 2H, $J = 7.0$ Hz), 3.68 (s, 3H), 3.65 (s, 3H), 2.53 (s, 3H), 1.25 (t, 3H, $J = 7.1$ Hz); ($M+H^+$) 358. Entry 12: ^{1}H NMR ($CDCl_3$): δ 8.55 (s, 1H), 7.66 (s, 1H), 7.52 (d, 2H, $J = 8.6$ Hz), 7.39 (d, 2H, $J = 8.6$ Hz), 4.49 (q, 2H, $J = 7.0$ Hz), 2.49 (s, 3H), 1.28 (t, 3H, $J = 7.0$ Hz), 1.26 (s, 9H); ($M+H^+$) 354. Entry 13: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 1H), 7.63 (s, 1H), 7.45 (d, 2H, $J = 7.5$ Hz), 7.32 (d, 1H, $J = 7.1$ Hz), 4.59 (q, 2H, $J = 6.5$ Hz), 2.69 (s, 3H), 1.42 (t, 3H, $J = 5.6$ Hz); ($M+H^+$) 366. Entry 14: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H), 7.53 (s, 1H), 7.27 (m, 4H), 3.08 (m, 1H), 2.71 (s, 3H), 2.23 (s, 3H), 1.35 (q, 2H, $J = 11$ Hz), 0.99 (m, 2H); ($M+H^+$) 324. Entry 15: ^{1}H NMR (300 MHz, CD_3OD): δ 8.76 (s, 1H), 7.87 (s, 1H), 7.53 (d, 2H, $J = 7.5$ Hz), 6.87 (d, 2H, $J = 7.4$ Hz), 3.04 (m, 1H), 2.70 (s, 3H), 1.32 (q, 2H, $J = 10.5$ Hz), 0.96 (m, 2H); ($M+H^+$) 326. Entry 16: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (s, 1H), 7.64 (d, 2H, $J = 7.1$ Hz), 7.63 (s, 1H), 6.95 (d, 2H, $J = 6.9$ Hz), 3.85 (s, 3H), 3.13 (m, 1H), 2.71 (s, 3H), 1.35 (q, 2H, $J = 10.8$ Hz), 0.96 (m, 2H); ($M+H^+$) 340. Entry 17: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (s, 1H), 7.61 (s, 1H), 6.93 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.05 (m, 1H), 2.69 (s, 3H), 1.34 (q, 2H, $J = 10.3$ Hz), 0.97 (m, 2H); ($M+H^+$) 370. Entry 18: ^{1}H NMR (300 MHz, CD_3OD): δ 8.60 (s, 1H), 7.65 (s, 1H), 7.63 (d, 2H, $J = 8.1$ Hz), 7.45 (d, 2H, $J = 7.5$ Hz), 3.03 (m, 1H), 2.67 (s, 3H), 1.34 (3, 11H), 0.93 (m, 2H); ($M+H^+$) 366. Entry 19: Trace observed via MS, no further data collected. Entry

20: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.68 (s, 1H), 7.58–7.48 (m, 3H), 7.33–7.28 (m, 6H), 2.30 (s, 3H), 2.20 (s, 9H);($M+H^+$) 360. Entry 21: ^{1}H NMR (300 MHz, CD_3OD): δ 8.64 (s, 1H), 7.85 (s, 1H), 7.42–7.29 (m, 5H), 7.15 (m, 2H), 6.56 (d, 2H, $J = 8.4$ Hz), 1.95 (s, 3H); ($M+H^+$) 362. Entry 22: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (s, 1H), 7.80–7.71 (m, 3H), 7.57–7.49 (m, 3H), 7.31 (m, 3H), 6.97 (m, 2H), 3.87 (s, 3H), 2.19 (s, 3H); ($M+H^+$) 376. Entry 23: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.88 (s, 1H), 7.58 (m, 3H), 7.38 (m, 2H), 6.98 (m, 2H), 5.39 (s, 1H), 3.87 (s, 6H), 2.27 (s, 3H); ($M+H^+$) 406. Entry 24: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.69 (s, 1H), 7.55 (m, 3H), 7.42–7.31 (m, 5H), 7.17 (m, 2H), 2.05 (s, 3H), 1.22 (s, 9H); ($M+H^+$) 402. Entry 25: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.70 (s, 1H), 7.53 (m, 3H), 7.42 (m, 2H), 7.31, (m, 3H), 2.21 (s, 3H); ($M+H^+$) 414. Entry 26: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.62 (s, 1H), 7.59 (d, 2H, $J = 6.1$ Hz), 7.28 (m, 7H), 5.78 (s, 2H), 2.70 (s, 3H), 2.28 (s, 3H); ($M+H^+$) 374. Entry 27: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (s, 1H), 7.61 (s, 1H), 7.52 (d, 2H, $J = 8.1$ Hz), 7.44 (d, 2H, $J = 6.1$ Hz), 7.27 (m, 3H), 6.80 (d, 2H, $J = 7.9$ Hz), 5.62 (s, 2H), 2.58 (s, 3H); ($M+H^+$) 376. Entry 28: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67 (s, 1H), 7.70 (s, 1H), 7.68 (d, 2H, $J = 7.7$ Hz), 7.56 (d, 2H, $J = 7.4$ Hz), 7.26 (m, 3H), 6.98 (d, 2H, $J = 7.9$ Hz), 5.75 (s, 2H), 3.88 (s, 3H), 2.65 (s, 3H); ($M+H^+$) 390. Entry 29: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H), 7.66 (s, 1H), 7.49 (d, 2H, $J = 6.5$ Hz), 7.27 (m, 3H), 6.89 (s, 3H), 5.66 (s, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 2.61 (s, 3H); ($M+H^+$) 420. Entry 30: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H), 7.69 (s, 1H), 7.62 (d, 2H, $J = 7.7$ Hz), 7.52 (d, 2H, $J = 6.4$ Hz), 7.46 (d, 2H, $J = 7.9$ Hz), 7.27 (m, 3H), 5.72 (s, 2H), 2.86 (s, 3H), 1.35 (s, 9H); ($M+H^+$) 416. Entry 31: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (s, 1H), 7.61 (s, 1H), 7.43 (m, 4H), 7.30 (m, 4H), 5.71 (s, 2H), 2.61 (s, 3H); ($M+H^+$) 428. Entry 32: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70 (s, 1H), 7.63 (s, 1H), 7.45 (d, 2H, $J = 7.5$ Hz), 7.32 (d, 1H, $J = 7.1$ Hz), 4.77 (m, 2H), 2.91 (m, 2H), 2.69 (s, 3H), 2.54 (br s, 6H); ($M+H^+$) 409.