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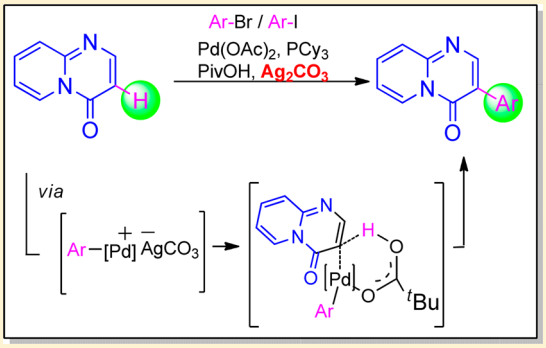
Pd-Catalyzed Ag(I)-Promoted C3-Arylation of Pyrido[1,2-*a*]pyrimidin-4-ones with Bromo/Iodo-Arenes

Sankar K. Guchhait* and Garima Priyadarshani

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), S. A. S. Nagar (Mohali) 160062, Punjab India

Supporting Information

ABSTRACT: A regioselective Ag(I)-promoted Pd-catalyzed C3−H activation−arylation of pyrido[1,2-*a*]pyrimidin-4-ones with bromo/iodo-(hetero)arenes under aqueous conditions has been developed. It affords an efficient access to pharmaceutically important versatile 3-aryl-pyrido[1,2-*a*]pyrimidin-4-ones. Interestingly, the arylation undergoes via a pathway with an unusual feature involving the formation of cationic arylpalladium species promoted by halo-sequestering Ag salts enabling concerted C3-palladation−deprotonation, as explored by relevant experiments and spectroscopic studies. The present approach is step economical, good yielding, and compatible with various functionalities and applicable to a wide range of starting materials.



The N-fused bicyclic heterocycles[1−5] have emerged as one of the most important heterocyclic frameworks because of their diverse applications in pharmaceuticals, agrochemicals, and material sciences.[6,7] In this family, pyrido[1,2-*a*]pyrimidin-4-one is an interesting scaffold displaying versatile biological activities,[8−10] such as CXCR3 antagonism,[11] MexAB-OprM-specific efflux pump inhibition,[12] acetylcholinesterase inhibition,[13] and HLE inhibition.[14] In particular, C3-arylated pyrido[1,2-*a*]pyrimidin-4-ones are often found as a valuable structural motif of a wide range of pharmaceutically active compounds, such as endothelial cell dysfunction inhibitors,[15] phosphoinositide 3-kinase inhibitors,[16] CXCR3 antagonists,[11] and cell growth inhibitors (Figure 1).[17] Also, they have been reported as mesoionic pesticides.[18] Pemirolast[19] is a marketed anti-allergic drug belonging to this class.

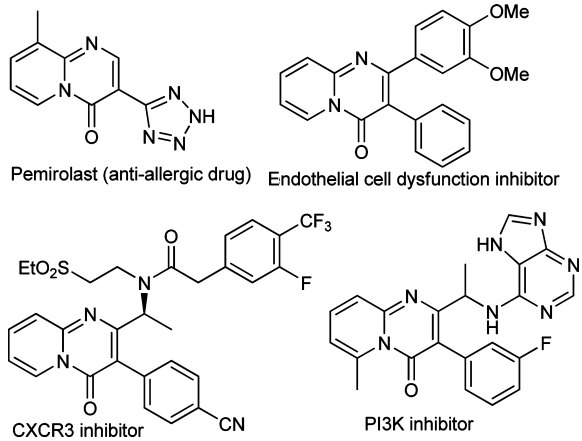


Figure 1. A representative examples of drugs/agents that possess 3-aryl-pyrido[1,2-*a*]-pyrimidin-4-one motif.

Despite of enormous importance, surprisingly, a few synthetic approaches to access C3-arylated pyrido[1,2-*a*]-pyrimidin-4-ones have been documented so far (Figure 2). Hermecz demonstrated an approach of classical intramolecular trans-amidation of 2-phenyl substituted enamine ester.[20] However, in the approach, a competing N → C acyl migration leading to formation of thermodynamically relatively more stable 1,8-naphthridine as major side product and requirement of harsh conditions and high heating were main limitations. The method of [4 + 2] cycloaddition of chlorophenylketene precursor with aminopyridine-derived imines providing 3-phenyl-pyrido[1,2-*a*]pyrimidin-4-ones is poor yielding.[21] In approach of Suzuki-coupling reaction[22] of C3-bromo/chloro derivatives of pyridopyrimidinones with arene boronic acids, the hydrodehalogenation reaction was found to compete to a significant extent. In addition, the coupling required a longer time up to 4 days and the use of a specific Pd−ligand complex as catalyst. The relative lower reactivity of C3-chloro/bromo derivatives of pyridopyrimidinone has been overcome later by using 3-iodo derivatives,[23] but the microwave irradiation for considerably longer time (2 h) was mandatory.

Remarkably, the pyrido[1,2-*a*]pyrimidin-4-one skeleton is known to possess several unusual chemical characteristics. Pyrido[1,2-*a*]pyrimidinones undergo thermal rearrangement via carbonyl ketene intermediates,[24] decomposition into aminopyridines in the harsh treatment with acids or bases,[20] and nucleophilic ring opening.[25,26] These susceptibility features of the skeleton are obviously the impeding factors for

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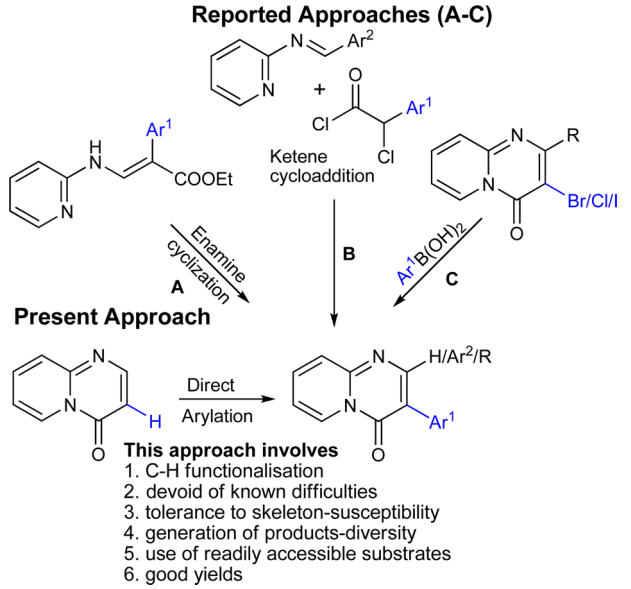


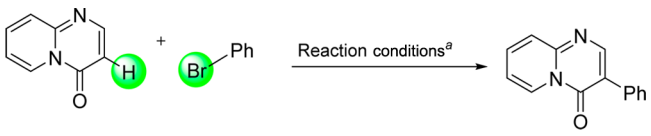
Figure 2. Reported approaches and the present route.

convenient preparation/derivatization of this class of compounds.

The direct arylation via C−H bond activation has significantly grown in the past decade and become one of the most widely explored reactions by the organic chemists.[27] These reactions are featured with instinct attractive qualities, a nonrequirement of prefunctionalization of arenes, avoidance of preparing organometallic coupling partners, atom-economical, and production of less waste. In this area, of the particular interest is the development of approach accommodating unexplored valuable heteroarenes as C−H partners.[28−30] Recently, Pd-catalyzed regioselective direct arylations have been documented for pharmaceutically important numerous N-fused heterocyclic motifs, for example, imidazo[1,2-*a*]-pyridines,[31] indolizines,[32] pyrazolo[1,5-*a*][1,3,5]triazin-4(3*H*)-ones,[33] imidazo[1,2-*a*]pyrazines,[34] and imidazo[1,2-*b*]-pyridazines.[35] These structural aryl-modulations of N-fused bicycles have been found useful in the discovery of new potent bioactive agents.[36,37] To the best of our knowledge, pyrido[1,2-*a*]pyrimidin-4-one, a privileged skeleton, has not been investigated yet for C−H bond functionalization-arylation. In the course of our continuous research on convenient and diversity feasible syntheses of pharmaceutically promising heterocyclic compounds, we were interested in the preparation of 3-aryl-pyrido[1,2-*a*]pyrimidin-4-ones. Herein, we report a Pd-catalyzed Ag(I)-promoted C3−H activation−arylation of pyrido[1,2-*a*]pyrimidin-4-one in aqueous cosolvent, affording a novel route to conveniently access versatile 3-aryl-pyrido[1,2-*a*]pyrimidin-4-ones. The mechanism involving a distinctive feature has been explored with relevant studies.

At the outset, the C3-arylation reactions of pyrido[1,2-*a*]pyrimidin-4-one following various Pd- and Cu-catalytic methods[38,39] developed for arylation of structurally related heterocycles with arene electrophiles (haloarenes and arene boronic acids) and a radical-based direct arylation[40] protocol were tried. However, the desired C3-arylated product was obtained in not more than 24% yield. Variation in reagents/conditions also could not improve the yield. Next, following our previously reported Pd-catalyzed method for direct arylation of imidazo[1,2-*a*]pyrazines with boromoarenes, a reaction of pyrido[1,2-*a*]pyrimidin-4-one with bromobenzene was performed.[34] The desired product was obtained in 13% yield only. Further studies with variation of the reagents/conditions of Pd-catalyzed method revealed that the use of cesium carbonate, $(^t\mathrm{Bu})_2\mathrm{PMe}\cdot\mathrm{HBF}_4$ and PivOH, gave the desired product in 26% yield. It also indicated that the use of pivalic acid is indispensable for this transformation. Therefore, subsequent evaluations were done using PivOH. The key results are summerized in the Table 1. The study of various

Table 1. Screening of Solvents, Ligands, Bases, And Additives[a]



no.	variable	temp (°C)	time (h)	yield (%)[b]
$Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (3 equiv), PivOH (30 mol %), $(^t\mathrm{Bu})_2\mathrm{PMe}\cdot\mathrm{HBF}_4$ (20 mol %), solvent (2 mL)				
1	DMF	110	48	24
2	DMA	110	2	8
3	NMP	110	2	10
4	MeCN	80	48	trace
5	toluene	110	6	35
6	1,4-dioxane	110	8	26
7	THF	80	24	trace
8	PEG-400	110	6	trace
$Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (3 equiv), PivOH (30 mol %), ligand (20 mol %), toluene				
9	BINAP	110	6	10
10	Xantphos	110	6	12
11	DavePhos	110	6	8
12	DPPM	110	6	15
13	DPPP	110	6	11
14	$(o\text{-tol})_3\mathrm{P}$	110	12	33
15	$(\mathrm{Cy})_3\mathrm{P}$	110	12	42
16	–	110	12	NR
17[c]	$Pd(PPh_3)_4$	110	24	12
$Pd(OAc)_2$ (10 mol %), $(\mathrm{Cy})_3\mathrm{P}$ (20 mol %), PivOH (30 mol %), base (3 equiv), toluene				
18	K_2CO_3	110	20	48
19	Na_2CO_3	110	20	15
20	$\mathrm{KO}^t\mathrm{Bu}$	110	20	NR
$Pd(OAc)_2$ (10 mol %), $(\mathrm{Cy})_3\mathrm{P}$ (20 mol %), K_2CO_3 (3 equiv), PivOH (30 mol %), Ag-salt (1 equiv), toluene				
21	AgOTf	110	20	65
22	AgOAc	110	20	61
23	Ag_2O	110	20	25
24	Ag_2CO_3	110	20	68

[a]Substrates, reagents and conditions: Pyridopyrimidine-4-one (0.5 mmol), PhBr (2 equiv). [b]Yield for maximum conversion in optimum time. [c]$Pd(OAc)_2$ was not used.

solvents ranging from weakly polar to polar aprotic or polar weakly protic showed a significant effect on the reaction (entries 1−8). In polar aprotic or weakly protic solvents (DMA, NMP, and PEG-400), the reaction completed within 2 h, but the side reactions were considerably high. When moderately polar solvents (acetonitrile and THF) were used, trace reaction conversions were observed. The side reactions were found to be little as a weakly polar solvent toluene was used, although the desired product was obtained in 35% yield due to incomplete conversion.

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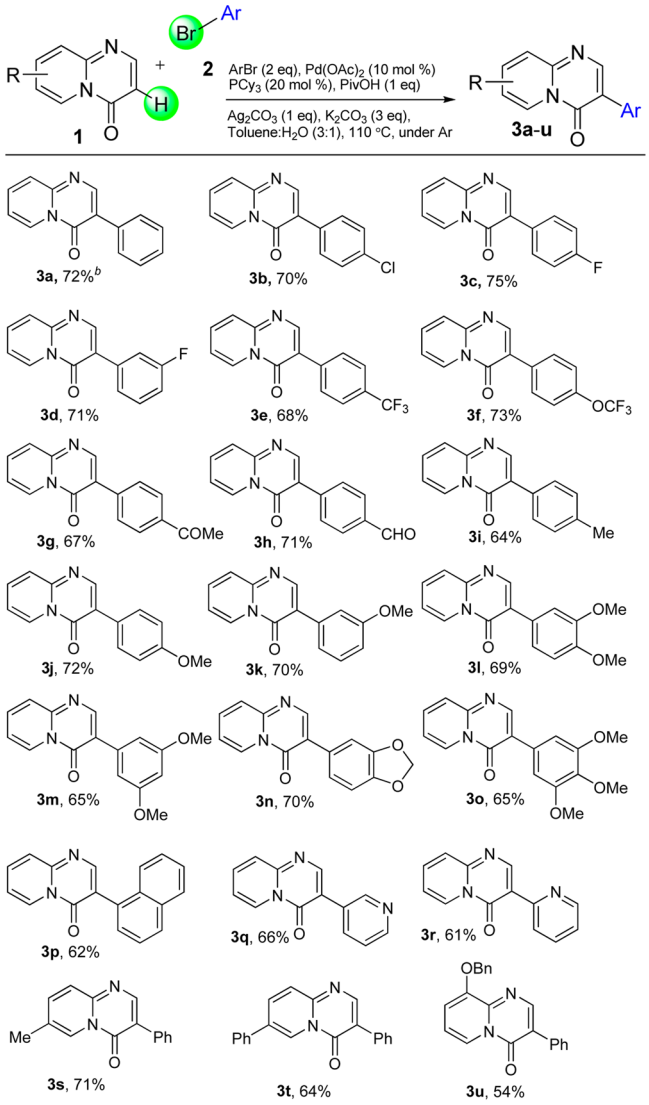
We then looked for evaluating different mono- and bidentate ligands (entries 9−15). Among the ligands tested, monodentate ligands were proved to be better, and tricyclohexylphosphine was the best, providing 42% yield. In the absence of a ligand, the reaction did not take place. Use of a Pd(0) catalyst precursor, $Pd(PPh_3)_4$ lowered the yield. In screening of bases, potassium carbonate was found to be more effective.

Fortunately, a significant improvement in the yield (65%) of the product was obtained by addition of a silver salt, AgOTf. This prompted us to investigate various silver salts (Table 1, entries 21−24). Silver carbonate was found to be the best (68% yield). When the reaction was performed in aqueous cosolvent (toluene-H_2O, 3:1) and with 1 equiv of pivalic acid, the yield enhanced to 72%. The reaction without pivalic acid provided virtually no arylation, indicating pivalate anion is necessary for this arylation.

With the developed protocol, we next investigated its generality toward generation of 3-aryl-pyrido[1,2-*a*]pyrimidin-4-ones with substitutions/functionalities diversities (Table 2). We were pleased to find that the protocol was flexible for versatile pyrido[1,2-*a*]pyrimidinones and bromoarenes, and the products were obtained in good yields. Bromoarenes bearing electron-withdrawing as well as electron-donating substituents and heteroaryl bromides were compatible. Unfortunately, the reaction did not work with pyridopyrimidinones with C2-substitutions, such as phenyl and methyl moieties. The reaction method also was found to be nonflexible to enable the arylation of 4*H*-pyrazino[1,2-*a*]pyrimidin-4-one. Gratifyingly, the functional groups like formyl, acetyl, benzyloxy, and dioxomethylene were tolerated under the reaction conditions. This provides an opportunity of their further derivatization toward preparation of products with elaborate substitution patterns. Importantly, the method did not produce any of regio-isomeric arylated and poly arylated products. The products that are known to be generated from ring opening/rearrangement/degradation of the skeleton did not form in the present method, as indicated by mass spectrometry of crude mixtures of several reactions. There was no oxidative homocoupling of pyridopyrimidinone, and the homocoupling of bromo-arenes occurred in traces for some cases. Iodobenzene provided a product yield (63%) as similar as that obtained using bromoarenes, while chlorobenzene was found to be nearly nonreactive. Aromatic alcohol derivatives, phenyl tosylate and phenyl triflate, were less reactive (7−12% yields). The reaction performed at 2 mmol scale did not cause a considerable decrease in the yield of the product.

We were then interested to gain knowledge inside the possible mechanism. The electronically varied substituents linked to bromoarenes showed nonsignificant influence on the reaction rate and yields, which ruled out the possibility of eletrophilic aromatic palladation (S_EAr) in the arylation. The Heck-type pathway would promote C2-arylation of pyrido[1,2-*a*]pyrimidinone due to more electron-rich at C3 of the nucleus. The presence of pivalate was found mandatory for the reaction. The observation is in accordance with the Pd-catalyzed C−H functionalization−arylation that occurs via concerted metalation deprotonation (CMD) pathway.[41−45] The ESI-MS (see SI) of three sets of reactions of pyridopyrimidinone with 4-bromotoluene, pyridopyrimidinone with 4-bromoanisole, and 7-methylpyridopyrimidinone with 4-bromobenzene suggested the formation of CMD transition state (Figure 3, TS C). IR studies of crude reaction mixtures obtained after intermediate times (2, 6, 10 h) were done, and no shift in C═O stretching

Table 2. Synthesis of 3-Arylpyridopyrimidinone[a]



[a]Substrates, reagents and condtions: Pyridopyrimidine-4-one (0.5 mmol), ArBr (2 equiv), $Pd(OAc)_2$ (10 mol %), PCy_3 (20 mol %), PivOH (1 equiv), Ag_2CO_3 (1 equiv), K_2CO_3 (3 equiv), toluene:water (3:1, 2 mL), 110 °C. [b]Yield for maximum conversion in optimum time.

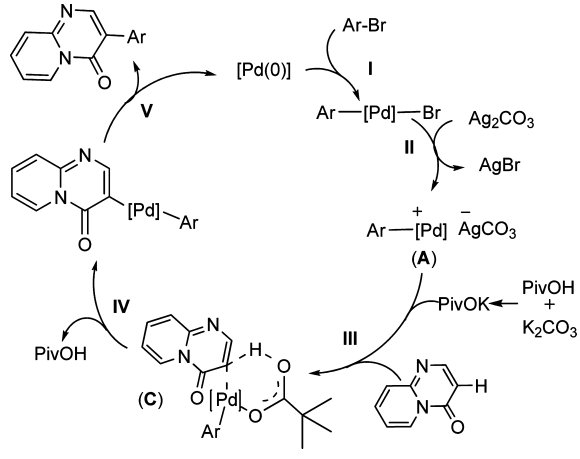


Figure 3. Plausible mechanism.

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frequency (1693 cm^{-1}) was observed (SI, spectra), indicating noninvolvement of C=O oxygen or π-bond chelation to Pd for C3-palladation or stabilization of TS.[46−48] The present reaction required stoichiometric Ag-salts, preferentially Ag_2CO_3. On the other hand, the reactions in the presence of oxidizing agents commonly used for Pd(II)−Pd(0) catalysis, such as $PhI(OAc)_2$, $Cu(OAc)_2$, or $K_2S_2O_8$, provided traces or no arylation product. Therefore, in this case, Ag_2CO_3 plays not as oxidizing agent but as halogen scavenger, an important function in the generation of cationic arylpalladium species. The formation of such highly reactive cationic species has been essential for reacting with pyridopyrimidinone in the presence of pivalate anion to enable C−H activation and C-palladation via construction of CMD TS. This is also supported by the fact that both of bromo- and iodo-arene required Ag_2CO_3 and were found to be similarly reactive arylating agents, although the poisoning[49] of Pd-catalyst is known to occur by iodide only. Based on these characteristics of the present reaction, a plausible mechanism is outlined (Figure 3). It involves the oxidative addition of ArBr to Pd(0), silver-promoted generation of cationic arylpalladium species, formation of CMD TS, and reductive elimination providing arylation product and regeneration of Pd(0).

In conclusion, we have developed for the first time a regioselective Pd-catalyzed Ag(I)-assisted direct C3−H activation−arylation of pyrido[1,2-*a*]pyrimidin-4-ones with bromo/iodo-(hetero)arenes en route to biologically relevant versatile 3-aryl-pyrido[1,2-*a*]pyrimidin-4-ones. Remarkably, the protocol is step-economical, general for various coupling partners, devoid of usual side reactions, overcomes the known difficulties due to skeleton susceptibility, and effective for preparing products in good yields under aqueous conditions, which are common limitations of the reported methods. Interestingly, in this direct arylation, the formation of cationic arylpalladium species assisted by Ag_2CO_3 as halo-sequestering agent was found to be essential for reaction with pyridopyrimidinone in the presence of pivalate anion and for promoting the C3-palladation−deprotonation; an unusual feature for CMD-based arylations and important for studying new reactions. This work is resourceful for expanded application of aryl-pyridopyrimidinones and will encourage for investigation of heteroarenes unexplored yet for C−H activation−arylation.

EXPERIMENTAL SECTION

General Information. Infrared (IR) spectra were recorded on a FTIR with ATR & IR Microscope spectrometer. ^1H NMR spectra were measured on a 400 MHz spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$/CD_3OD/DMSO-d_6 integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, td = triplet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, br = broad), and coupling constants (Hz). ^{13}C NMR spectra were measured on a 100 MHz spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High-resolution mass spectra (HRMS) were performed on a high-resolution LCMS/MS instrument with "Q-TOF" mass analyzer. For thin-layer chromatography (TLC) analysis throughout this work, commerical supplier precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. The products were purified by column chromatography silica gel 60−120 (silica gel 60−120 mesh, neutral, spherical).

The starting materials and solvents were used as received from commercial suppliers without further purification.

General Experimental Procedure for Direct C3-Arylation of Pyrido[1,2-*a*]pyrimidinones. Pyridopyrimidinone (0.5 mmol), K_2CO_3 (1.5 mmol, 207 mg, 3 equiv), Ag_2CO_3 (0.5 mmol, 137 mg, 1 equiv), PCy_3 (0.1 mmol, 28 mg, 0.2 equiv), and $Pd(OAc)_2$ (0.05 mmol, 11 mg, 0.1 equiv) were weighed in air to a sealed tube equipped with magnetic stirring bar. PivOH (0.5 mmol, 0.06 mL, 1 equiv) and bromoarene (1 mmol, 2 equiv) were added to the tube. The tube was purged with argon, and toluene (1.5 mL) and water (0.5 mL) were added to the resultant mixture. The mixture was heated at 110 °C for 18−24 h until complete consumption of the substrate as indicated by TLC. It was then cooled to rt and concenterated under reduced pressure. The mixture was extracted with EtOAc (2 × 50 mL) and washed with 10% aqueous ammonia solution (3 × 20 mL). The combined organic solution was washed with water (2 × 5 mL) and brine (1 × 5 mL), dried with anhyd. Na_2SO_4, and concentrated under reduced pressure. The column chromatographic purification of crude mass was performed on silica gel partially deacidified by passing triethylamine (1−2 mL) using EtOAc-hexane (25−40%) as eluting solvent to afford the arylated products (**3a−3u**).

3-Phenyl-4H-pyrido[1,2-a]pyrimidin-4-one[22] ***(3a)***. Yellow crystalline solid, 80 mg, 72%, mp 167−169 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.20 (d, J = 7.1 Hz, 1H), 8.55 (s, 1H), 7.80 (d, J = 7.1 Hz, 2H), (m, 2H), 7.76−7.72 (m, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.46 (dd, J = 7.8 Hz, J = 7.4 Hz, 2H), 7.36 (t, J = 6.7 Hz, 1H), 7.19 (dt, J = 7.2 Hz, J = 1.6 Hz, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.8, 152.9, 150.7, 135.7, 134.3, 128.5, 127.8, 127.7, 126.5, 117.0, 115.9 ppm; IR: ν_{max} 3136, 1668, 1630, 1494 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{14}H_{11}N_2O$ $[M + H]^+$ 223.0871, found: 223.0864.

3-(4-Chlorophenyl)-4H-pyrido[1,2-a]pyrimidin-4-one ***(3b)***. Yellow solid, 89 mg, 70%, mp 198−200 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.20 (ddd, J = 7.2 Hz, J = 1.5 Hz, J = 0.8 Hz, 1H), 8.54 (s, 1H), 7.80−7.73 (m, 3H), 7.71 (ddd, J = 8.9 Hz, J = 1.4 Hz, J = 0.8 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.23 (dt, J = 7.2 Hz, J = 1.5 Hz, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.6, 152.8, 150.8, 135.9, 133.7, 132.7, 129.7, 128.7, 127.7, 126.6, 116.1, 115.8 ppm; IR: ν_{max} 3136, 1668, 1630, 1494, 764 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{14}H_{10}ClN_2O$ $[M(^{35}Cl) + H]^+$ 257.0481, found: 257.0474.

3-(4-Fluorophenyl)-4H-pyrido[1,2-a]pyrimidin-4-one ***(3c)***. Yellow solid, 102 mg, 75%, mp >200 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.19 (ddd, J = 7.1 Hz, J = 1.4 Hz, J = 0.8 Hz, 1H), 8.52 (s, 1H), 7.80−7.74 (m, 3H), 7.70 (ddd, J = 8.9 Hz, J = 1.4 Hz, J = 0.8 Hz, 1H), 7.21 (dt, J = 7.2 Hz, J = 1.6 Hz, 1H), 7.15 (t, J = 8.8 Hz, 2H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 162.4 (d, J_{C-F} = 246 Hz), 156.8, 152.7, 150.7, 135.7, 130.23 (d, $J_{C-C-C-F}$ = 8 Hz), 130.23, 127.7, 126.6, 116.1, 115.9, 115.5 (d, J_{C-C-F} = 21 Hz) ppm; IR: ν_{max} 2924, 1672, 1634, 1484, 1298 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{14}H_{10}FN_2O$ $[M + H]^+$ 241.0777, found: 241.0774.

3-(3-Fluorophenyl)-4H-pyrido[1,2-a]pyrimidin-4-one ***(3d)***. Light-yellow solid, 85 mg, 71%, mp 170−172 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.21 (ddd, J = 7.2 Hz, J = 1.4 Hz, J = 0.7 Hz, 1H), 8.56 (s, 1H), 7.78 (dt, J = 6.6 Hz, J = 1.6 Hz, 1H), 7.71 (ddd, J = 8.8 Hz, J = 1.2 Hz, J = 0.8 Hz, 1H), 7.61−7.55 (m, 2H), 7.44−7.40 (m, 1H), 7.23 (dt, J = 7.1 Hz, J = 1.5 Hz, 1H), 7.15 (ddd, J = 8.4 Hz, J = 2.6 Hz, J = 0.9 Hz, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 162.8 (d, J_{C-F} = 244 Hz), 156.6, 153.1, 150.9, 136.4 (d, $J_{C-C-C-F}$ = 9 Hz), 136.1, 129.9 (d, $J_{C-C-C-F}$ = 8 Hz), 127.8, 126.6, 123.9 (d, $J_{C-C-C-C-F}$ = 3 Hz), 116.1, 115.5 (d, J_{C-C-F} = 23 Hz), 114.6 (d, J_{C-C-F} = 21 Hz) ppm; IR: ν_{max} 3136, 3057, 1675, 1628, 1476, 1293 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{14}H_{10}FN_2O$ $[M + H]^+$ 241.0777, found: 241.0767.

3-(4-(Trifluoromethyl)phenyl)-4H-pyrido[1,2-a]pyrimidin-4-one[22] ***(3e)***. Light-yellow solid, 98 mg, 68%, mp >200 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.22 (ddd, J = 7.2 Hz, J = 1.4 Hz, J = 0.8 Hz, 1H), 8.58 (s, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.82 (dt, J = 6.6 Hz, J = 1.5 Hz, 1H), 7.74−7.70 (m, 3H), 7.27−7.23 (m, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.6, 153.3, 151.1, 137.9, 136.4, 129.6 (q, J_{C-C-F} = 32 Hz), 128.6, 127.8, 126.6, 125.4 (q, $J_{C-C-C-F}$ = 4 Hz), 124.2 (q, J_{C-F} = 270 Hz), 116.3, 115.4 ppm; IR: ν_{max} 3108, 1666, 1633, 1492, 1102, 1071 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{15}H_{10}F_3N_2O$ $[M + H]^+$ 291.0745, found: 291.0745.

3-(4-(Trifluoromethoxy)phenyl)-4H-pyrido[1,2-a]pyrimidin-4-one ***(3f)***. Light-yellow solid, 111 mg, 73%, mp 175−177 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.21 (ddd, J = 7.2 Hz, J = 1.4 Hz, J = 0.8 Hz, 1H), 8.55 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.79 (ddd, J = 8.9 Hz, J = 6.5

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J. Org. Chem. 2015, 80, 8482−8488

Hz, J = 1.5 Hz, 1H), 7.71 (dd, J = 8.8 Hz, J = 0.8 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.24 (dt, J = 7.1 Hz, J = 1.5 Hz, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.7, 152.9, 150.9, 148.7, (d, $J_{C-O-C-F}$ = 2 Hz), 136.0, 133.0, 129.9, 127.7, 126.6, 121.0, 120.5 (q, J_{C-F} = 256 Hz), 116.1, 115.6 ppm; IR: ν_{max} 3108, 1669, 1632, 1497, 1295, 1203, 1146 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{15}H_{10}F_3N_2O_2$ $[M + H]^+$ 307.0694, found: 307.0688.

3-(4-Acetylphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (**3g**). Light-yellow solid, 88 mg, 67%, mp >200 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.23 (ddd, J = 7.1 Hz, J = 1.4 Hz, J = 0.7 Hz, 1H), 8.61 (s, 1H), 8.05 (d, J = 8.6 Hz, 2H), 7.94 (d, J = 8.6 Hz, 2H), 7.84−7.79 (m, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.28−7.24 (m, 1H), 2.65 (s, 3H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 197.7, 156.5, 153.4, 151.1, 139.2, 136.4, 136.0, 128.6, 128.4, 127.8, 126.7, 116.3, 115.6, 26.7 ppm; IR: ν_{max} 3073, 1672, 1630, 1491 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{16}H_{13}N_2O_2$ $[M + H]^+$ 265.0977, found: 265.0973.

3-(4-Formylphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (**3h**). Yellow crystalline solid, 88 mg, 71%, mp 165−167 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 10.05 (s, 1H), 9.24 (d, J = 6.9 Hz, 1H), 8.63 (s, 1H), 8.02 (d, J = 8.3 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 7.85−7.81 (m, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.27 (ddd, J = 8.3 Hz, J = 6.8 Hz, J = 1.2 Hz, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 191.9, 156.5, 153.5, 151.2, 140.7, 136.6, 135.3, 129.9, 128.8, 127.9, 126.7, 116.4, 115.3 ppm; IR: ν_{max} 3047, 2835, 2733, 1694, 1668, 1632, 1484 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{15}H_{11}N_2O_2$ $[M + H]^+$ 251.0820, found: 251.0818.

3-(4-Methylphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (**3i**). Yellow crystals, 75 mg, 64% yield, mp 142−144 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.19 (ddd, J = 7.2 Hz, J = 1.4 Hz, J = 0.8 Hz, 1H), 8.54 (s, 1H), 7.74−7.66 (m, 4H), 7.27 (d, J = 7.9 Hz, 2H), 7.20−7.16 (m, 1H), 2.40 (s, 3H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.8, 152.6, 150.5, 137.7, 135.4, 131.3, 129.2, 128.4, 127.7, 126.5, 117.1, 115.7, 21.3 ppm; IR: ν_{max} 3136, 3027, 2920, 1668, 1630, 1485 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{15}H_{13}N_2O$ $[M + H]^+$ 237.1028, found: 237.1022.

3-(4-Methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one[22] (**3j**). Yellow crystals, 90 mg, 72% yield, mp 142−144 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.18 (dd, J = 7.2 Hz, J = 1.1 Hz, 1H), 8.52 (s, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.73−7.69 (m, 1H), 7.67 (ddd, J = 8.9 Hz, J = 1.5 Hz, J = 0.8 Hz, 1H), 7.19−7.15 (m, 1H), 7.00 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 159.3, 156.9, 152.2, 150.3, 135.3, 129.7, 127.6, 126.6, 126.5, 116.9, 115.7, 114.0, 55.4 ppm; IR: ν_{max} 2955, 2924, 1674, 1632, 1482, 1245, 1179 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{15}H_{13}N_2O_2$ $[M + H]^+$ 253.0977, found: 253.0974.

3-(3-Methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (**3k**). Yellow solid, 88 mg, 70% yield, mp 130−132 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.18 (d, J = 7.2 Hz, 1H), 8.56 (d, J = 1.6 Hz, 1H), 7.75 (dt, J = 6.6 Hz, J = 1.5 Hz, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.40−7.35 (m, 3H), 7.19 (dt, J = 6.5 Hz, J = 1.5 Hz, 1H), 6.93−6.90 (m, 1H), 3.86 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 159.6, 156.7, 153.0, 150.7, 135.7, 135.6, 129.5, 127.7, 126.5, 120.9, 116.8, 115.9, 114.1, 113.6, 55.3 ppm; IR: ν_{max} 3080, 2937, 1674, 1497, 1282, 1041 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{15}H_{13}N_2O_2$ $[M + H]^+$ 253.0977, found: 253.0971.

3-(3,4-Dimethoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (**3l**). Yellow solid, 97 mg, 69% yield, mp 155−157 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.19 (d, J = 7.1 Hz, 1H), 8.55 (s, 1H), 7.74 (dt, J = 6.4 Hz, J = 1.5 Hz, 1H), 7.69 (dd, J = 8.8 Hz, J = 0.6 Hz, 1H), 7.47 (d, J = 2 Hz, 1H), 7.32 (dd, J = 8.3 Hz, J = 2 Hz, 1H), 7.19 (dt, J = 7.3 Hz, J = 1.6 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.9, 152.4, 150.3, 148.9, 148.8, 135.3, 127.5, 126.9, 126.5, 120.9, 116.8, 115.8, 111.9, 111.3, 55.9 ppm; IR: ν_{max} 2956, 1672, 1630, 1479, 1277, 1024 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{16}H_{15}N_2O_3$ $[M + H]^+$ 283.1082, found: 283.1078.

3-(3,5-Dimethoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (**3m**). Yellow solid, 91 mg, 65% yield, mp 135−137 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.19 (ddd, J = 7.2 Hz, J = 1.3 Hz, J = 0.8 Hz, 1H), 8.56 (s, 1H), 7.76 (ddd, J = 8.9 Hz, J = 6.5 Hz, J = 1.6 Hz, 1H), 7.69 (ddd, J = 8.9 Hz, J = 1.3 Hz, J = 0.8 Hz, 1H), 7.20 (ddd, J = 7.1 Hz, J = 6.5 Hz, J = 1.5 Hz, 1H), 6.97 (d, J = 2.3 Hz, 2H), 6.49 (t, J = 2.3 Hz, 1H), 3.85 (s, 6H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 160.8, 156.6, 153.0, 150.7, 136.2, 135.8, 127.7, 126.5, 116.8, 115.9, 106.7, 100.2, 55.4 ppm; IR: ν_{max} 2936, 1681, 1632, 1485, 1158, 1046 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{16}H_{15}N_2O_3$ $[M + H]^+$ 283.1082, found: 283.1077.

3-(Benzo[d][1,3]dioxol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**3n**). Yellow solid, 93 mg, 70%, mp >200 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.19 (dd, J = 7.2 Hz, J = 0.4 Hz, 1H), 8.49 (s, 1H), 7.74 (ddd, J = 8.9 Hz, J = 6.4 Hz, J = 1.5 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 1.7 Hz, 1H), 7.24 (dd, J = 8.1 Hz, J = 1.7 Hz, 1H), 7.19 (dt, J = 7.2 Hz, J = 1.6 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.00 (s, 2H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.8, 152.4, 150.4, 147.8, 147.4, 135.4, 128.1, 127.6, 126.5, 122.3, 116.9, 115.8, 109.1, 108.5, 101.2 ppm; IR: ν_{max} 3029, 2905, 1677, 1633, 1498, 1448, 1251, 1035 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{15}H_{11}N_2O_3$ $[M + H]^+$ 267.0769, found: 267.0765.

3-(3,4,5-Trimethoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (**3o**). Yellow solid, 101 mg, 65%, mp 170−172 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.19 (ddd, J = 7.1 Hz, J = 1.5 Hz, J = 0.8 Hz, 1H), 8.56 (s, 1H), 7.76 (ddd, J = 8.9 Hz, J = 6.4 Hz, J = 1.5 Hz, 1H), 7.71 (ddd, J = 8.9 Hz, J = 1.5 Hz, J = 0.8 Hz, 1H), 7.22 (ddd, J = 8.0 Hz, J = 6.5 Hz, J = 1.6 Hz, 1H), 7.05 (s, 2H), 3.93 (s, 6H), 3.90 (s, 3H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.8, 153.2, 152.7, 150.6, 137.9, 135.7, 129.8, 127.6, 126.9, 116.9, 115.9, 105.9, 60.9, 56.2 ppm; IR: ν_{max} 2996, 1666, 1632, 1485, 1246, 1120 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{17}H_{17}N_2O_4$ $[M + H]^+$ 313.1188, found: 313.1184.

3-(Naphthalen-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**3p**). Yellow solid, 87 mg, 62% yield, mp 123−125 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.21 (d, J = 7.1 Hz, 1H), 8.49 (s, 1H), 7.94−7.90 (m, 2H), 7.82−7.74 (m, 3H), 7.58−7.43 (m, 4H), 7.22 (dt, J = 7.2 Hz, J = 1.9 Hz, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 157.1, 154.9, 151.3, 136.0, 133.8, 132.1, 132.0, 128.9, 128.5, 128.4, 127.9, 126.6, 126.2, 125.9, 125.6, 125.5, 117.1, 115.9 ppm; IR: ν_{max} 3036, 2926, 1678, 1638, 1483 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{18}H_{13}N_2O$ $[M + H]^+$ 273.1028, found: 273.1025.

3-(Pyridin-3-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**3q**). Yellow solid, 73 mg, 66%, mp 170−172 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.21 (ddd, J = 7.2 Hz, J = 1.4 Hz, J = 0.8 Hz, 1H), 8.97 (dd, J = 2.2 Hz, J = 0.6 Hz, 1H), 8.60 (dd, J = 4.8 Hz, J = 1.6 Hz, 1H), 8.59 (s, 1H), 8.22 (ddd, J = 7.9 Hz, J = 2.2 Hz, J = 1.7 Hz, 1H), 7.82 (ddd, J = 8.8 Hz, J = 6.6 Hz, J = 1.5 Hz, 1H), 7.74 (ddd, J = 8.8 Hz, J = 1.4 Hz, J = 0.8 Hz, 1H), 7.40 (ddd, J = 7.9 Hz, J = 4.8 Hz, J = 0.7 Hz, 1H), 7.28−7.24 (m, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.7, 152.9, 151.1, 149.0, 148.7, 136.4, 135.9, 130.3, 127.7, 126.7, 123.3, 116.3, 113.7 ppm; IR: ν_{max} 3115, 1682, 1632, 1573, 1503 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{13}H_{10}N_3O$ $[M + H]^+$ 224.0824, found: 224.0819.

3-(Pyridin-2-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**3r**). Yellow solid, 68 mg, 61%, mp 160−162 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.40 (s, 1H), 9.28 (ddd, J = 7.2 Hz, J = 1.3 Hz, J = 0.8 Hz, 1H), 8.69 (ddd, J = 4.7 Hz, J = 1.7 Hz, J = 0.8 Hz, 1H), 8.54 (dd, J = 8.1 Hz, J = 0.8 Hz, 1H), 7.84−7.75 (m, 3H), 7.28−7.22 (m, 2H) ppm; $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 156.6, 155.2, 152.3, 151.3, 149.3, 136.4, 127.9, 126.8, 123.5, 122.2, 116.3, 114.1 ppm; IR: ν_{max} 3106, 3031, 1678, 1631, 1567, 1485 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{13}H_{10}N_3O$ $[M + H]^+$ 224.0824, found: 224.0818.

7-Methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (**3s**). Yellow solid, 84 mg, 71%, mp 110−113 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.52 (s, 1H), 7.79 (d, J = 7.3 Hz, 2H), 7.64−7.58 (m, 2H), 7.46 (dd, J = 7.8 Hz, J = 7.5 Hz, 2H), 7.35 (t, J = 7.4 Hz, 1H), 2.46 (s, 3H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.5, 152.6, 149.6, 138.6, 134.5, 128.52, 128.49, 127.6, 126.2, 125.9, 125.1, 116.6, 18.4 ppm; IR: ν_{max} 3057, 1677, 1636, 1478 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{15}H_{13}N_2O$ $[M + H]^+$ 237.1028, found: 237.1024.

3,7-Diphenyl-4H-pyrido[1,2-a]pyrimidin-4-one (**3t**). Yellow solid, 95 mg, 64%, mp 166−168 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.41 (dd, J = 2.0 Hz, J = 0.4 Hz, 1H), 8.56 (s, 1H), 8.02 (dd, J = 9.2 Hz, J = 2.1 Hz, 1H), 7.81 (d, J = 7.1 Hz 2H), 7.77 (d, J = 9.2 Hz, 1H), 7.67 (d, J = 7.1 Hz 2H), 7.55−7.51 (m, 2H), 7.49−7.44 (m, 3H), 7.46 (dd, J = 7.5 Hz, J = 7.3 Hz, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.9, 152.7, 149.7, 135.7, 135.5, 134.3, 129.9, 129.4, 128.9, 128.5, 127.8, 126.9, 126.6, 124.7, 117.0 ppm; IR: ν_{max} 3056, 1675, 1635, 1477

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J. Org. Chem. 2015, 80, 8482−8488

cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{20}H_{14}N_2ONa$ $[M + Na]^+$ 321.1004, found: 321.0997.

*9-(Benzyloxy)-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (**3u**).* Light-yellow solid, 88 mg, 54%, mp 150−152 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.81 (ddd, J = 4.1 Hz, J = 3.5 Hz, J = 0.9 Hz, 1H), 8.60 (s, 1H), 7.80 (d, J = 7.2 Hz, 2H), 7.49−7.44 (m, 4H), 7.41−7.32 (m, 4H), 7.03−6.99 (m, 2H), 5.40 (s, 2H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 156.9, 151.7, 151.2, 145.1, 135.2, 134.2, 128.9, 128.6, 128.5, 127.9, 127.2, 119.7, 117.8, 114.7, 112.9, 71.7 ppm; IR: ν_{max} 3159, 3058, 2926, 1670, 1634, 1480, 1297, 1266, 1144 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{21}H_{17}N_2O_2$ $[M + H]^+$ 329.1290, found: 329.1288.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01573.

ESI-MS of crude reaction mixtures, scanned ^1H and ^{13}C spectra for products **3a**−**3u** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Email: skguchhait@niper.ac.in. Tel: 91 (0)172 2214683. Fax: 91 (0)172 2214692.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Bagdi, A. K.; Santra, S.; Monira, K.; Hajra, A. *Chem. Commun.* **2015**, *51*, 1555−1575.

(2) Baviskar, A. T.; Madaan, C.; Preet, R.; Mohapatra, P.; Jain, V.; Agarwal, A.; Guchhait, S. K.; Kundu, C. N.; Banerjee, U. C.; Bharatam, P. V. *J. Med. Chem.* **2011**, *54*, 5013−5030.

(3) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433−3436.

(4) Chernyak, D.; Gadamsetty, S. B.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 2307−2310.

(5) Thiel, O. R.; Achmatowicz, M. M.; Reichelt, A.; Larsen, R. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8395−8398.

(6) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347−361.

(7) Quin, L. D.; Tyrell, J. A. *The Importance of Heterocycles in Medicine: Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals*; John Wiley & Sons, Inc.: Hoboken, NJ, 2010; pp 196−219.

(8) Nakayama, K.; Kawato, H.; Watanabe, J.; Ohtsuka, M.; Yoshida, K.; Yokomizo, Y.; Sakamoto, A.; Kuru, N.; Ohta, T.; Hoshino, K.; Yoshida, K.; Ishida, H.; Cho, A.; Palme, M. H.; Zhang, J. Z.; Lee, V. J.; Watkins, W. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 475−479.

(9) Nakayama, K.; Kuru, N.; Ohtsuka, M.; Yokomizo, Y.; Sakamoto, A.; Kawato, H.; Yoshida, K.; Ohta, T.; Hoshino, K.; Akimoto, K.; Itoh, J.; Ishida, H.; Cho, A.; Palme, M. H.; Zhang, J. Z.; Lee, V. J.; Watkins, W. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2493−2497.

(10) Roma, G.; Cinone, N.; Di Braccio, M.; Grossi, G.; Leoncini, G.; Signorello, M. G.; Carotti, A. *Bioorg. Med. Chem.* **2000**, *8*, 751−768.

(11) Li, A.-R.; Johnson, M. G.; Liu, J.; Chen, X.; Du, X.; Mihalic, J. T.; Deignan, J.; Gustin, D. J.; Duquette, J.; Fu, Z.; Zhu, L.; Marcus, A. P.; Bergeron, P.; McGee, L. R.; Danao, J.; Lemon, B.; Carabeo, T.; Sullivan, T.; Ma, Ji.; Tang, L.; Tonn, G.; Collins, T. L.; Medina, J. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 688−693.

(12) Nakayama, K.; Ishida, Y.; Ohtsuka, M.; Kawato, H.; Yoshida, K.-i.; Yokomiza, Y.; Ohta, T.; Hoshino, K.; Otani, T.; Kurosaka, Y.; Yoshida, K.; Ishida, H.; Lee, V. J.; Renau, T. E.; Watkins, W. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4205−4208.

(13) Sadashiva, C. T.; Chandra, J. N. N. S.; Ponnappa, K. C.; Gowda, T. V.; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3932−3936.

(14) Varga, M.; Kapui, Z.; Bátori, S.; Nagy, L. T.; Vasvári-Debreczy, L.; Mikus, E.; Urbán-Szabó, K.; Arányi, P. *Eur. J. Med. Chem.* **2003**, *38*, 421−425.

(15) Turco, S. D.; Sartini, S.; Sentieri, C.; Saponaro, C.; Navarra, T.; Dario, B.; Settimo, F. D.; Motta, C. L.; Basta, G. *Eur. J. Med. Chem.* **2014**, *72*, 102−109.

(16) Li, Y.-L.; Metcalf, B. W.; Combs, A. P. Pyrimidinones as pi3k inhibitors. EP2448938, June 10, 2015.

(17) Yao, P.; Zhai, X.; Liu, D.; Qi, B. H.; Tan, H. L.; Jin, Y. C.; Gong, P. *Arch. Pharm.* **2010**, *343*, 17−23.

(18) Kawashima, T.; Iwamoto, I.; Nakagawa, N.; Tomioka, H.; Yoshida, S. *Int. Arch. Allergy Immunol.* **1994**, *103*, 405−409.

(19) Holyoke, C. W.; Tong, M.-H. T.; Coats, R. A.; Zhang, W.; McCann, S. F.; Chan, D. M.-T. Mediated ion pesticides. CN101939302, October 29, 2014.

(20) Hermecz, I.; Mészáros, Z.; Vasvári-Debreczy, L.; Horváth, Á.; Horváth, G.; Pongor-Csákvári, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, *7*, 789−795.

(21) Katagiri, N.; Kato, T.; Niwa, R. *J. Heterocycl. Chem.* **1984**, *21*, 407−412.

(22) Molnár, A.; Kapros, A.; Párkányi, L.; Mucsi, Z.; Vlád, G.; Hermecz, I. *Org. Biomol. Chem.* **2011**, *9*, 6559−6565.

(23) Kabri, Y.; Crozet, M. D.; Primas, N.; Vanelle, P. *Eur. J. Med. Chem.* **2012**, *28*, 5595−5604.

(24) Schober, B. D.; Kappe, T. *J. Heterocycl. Chem.* **1988**, *25*, 1231−1236.

(25) Lappin, G. R. *J. Am. Chem. Soc.* **1949**, *71*, 3258−3259.

(26) Náray-Szabó, G.; Hermecz, I.; Mészáros, Z. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1753−1756.

(27) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369−375.

(28) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1770.

(29) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238.

(30) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169.

(31) Choy, P. Y.; Luk, K. C.; Wu, Y.; So, C. M.; Wang, L.-l.; Kwong, F. Y. *J. Org. Chem.* **2015**, *80*, 1457−1463.

(32) Liu, B.; Wang, Z.; Wu, N.; Li, M.; You, J.; Lan, J. *Chem. - Eur. J.* **2012**, *18*, 1599−1603.

(33) Long, J.; Lee, W.-S.; Chough, C.; Bae, H.; Kim, B. M. *J. Org. Chem.* **2015**, *80*, 4716−4721.

(34) Guchhait, S. K.; Kandekar, S.; Kashyap, M.; Taxak, N.; Bharatam, P. V. *J. Org. Chem.* **2012**, *77*, 8321−8328.

(35) Akkaoui, A. E.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Eur. J. Org. Chem.* **2010**, *2010*, 862−871.

(36) Baviskar, A. T.; Amrutkar, S. M.; Trivedi, N.; Chaudhary, V.; Nayak, A.; Guchhait, S. K.; Banerjee, U. C.; Bharatam, P. V.; Kundu, C. N. *ACS Med. Chem. Lett.* **2015**, *6*, 481−485.

(37) Zaleplon, a 7-aryl substituted pyrazolo[1,5-*a*]pyrimidine derivative, is a marketed drug used for the management/treatment of insomnia. In the class of 2-arylated imidazo[1,2-*a*]pyridines, there are several marketed drugs, for example, Zolpidem and Zolimidine.

(38) Čerňová, M.; Čerňa, I.; Pohl, R.; Hocek, M. *J. Org. Chem.* **2011**, *76*, 5309−5319.

(39) Kim, Y. W.; Niphakis, M. J.; Georg, G. I. *J. Org. Chem.* **2012**, *77*, 9496−9503.

(40) Guchhait, S. K.; Kashyap, M.; Saraf, S. *Synthesis* **2010**, *2010*, 1166−1170.

(41) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754−8756.

(42) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066−1067.

DOI: 10.1021/acs.joc.5b01573
J. Org. Chem. 2015, 80, 8482−8488

(43) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496−16497.
(44) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880−6886.
(45) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118−1126.
(46) Gandeepan, P.; Parthasarathy, K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8569−8571.
(47) Li, H.; Zhu, R.-Y.; He, K.-H.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 4850−4853.
(48) Gandeepan, P.; Hung, C.-H.; Cheng, C.-H. *Chem. Commun.* **2012**, *48*, 9379−9381.
(49) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581−590.

DOI: 10.1021/acs.joc.5b01573
J. Org. Chem. 2015, 80, 8482−8488