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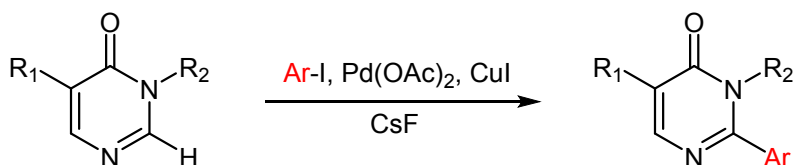


**Ortho-directed Palladium-catalyzed Direct C-H
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Keywords:	arylation, palladium, catalysis, Suzuki coupling, pyrimidinone
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Ortho-directed Palladium-catalyzed Direct C-H Functionalization of *N*-picolinyl and 2-cyanoethyl Pyrimidinones with Aryl Halides

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20 examples, R₁ = H, OMe or Ar group, R₂ = ortho-directing and protecting group, up to 75 % yield

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Abstract The ortho-directed palladium-catalyzed direct C-H arylation of *N*-picolinyl pyrimidin-4-one was achieved with various aryl halides. The methodology was extended towards C-H arylation of pyrimidin-4-ones incorporating methoxy group and aryl groups at C5 site. The 2-cyanoethyl was also evaluated as ortho-directed group. The methodology gives access to innovative *N*-substituted 2- and 2,5-diarylated pyrimidin-4-ones. The standard 3-step deprotection sequence of picolinyl group was also studied.

Key words catalysis, palladium, CH-arylation, Suzuki coupling, pyrimidinone

The transition-metal catalyzed direct C-H functionalization of heterocycles has emerged as powerful complementary attractive atom- and step-economical synthetic alternative to the conventional cross-coupling reactions.¹ The methodology is especially required when halogenated or metalated heterocycles are unavailable or to open the chemical space of functionalization (site-diversity). To date, the important families of 1,3-diazol-4-one non-aromatic heterocycles such as quinazolinone, pyrimidinone, imidazolone and imidazopyrimidinone (hypoxanthine), which are intensively used in pharmaceutical sciences as biomolecules (**Figure 1**),² are mainly prepared through various condensation reactions.³ In the field of palladium-catalyzed C-C formation, only the Liebeskind-Srogl cross-coupling of C2-halogenated diazol-4-ones with boronic acids is reported.^{4,5} Moreover the direct C-H functionalization of 1,3-diazolone non aromatic heterocycles

remains highly sparsely investigated. Harayama first reported the palladium-catalyzed intramolecular direct C2-H heteroarylation of the *N*-methyl-2-bromoquinolin-3-yl quinazolinone to achieve the neat total synthesis of Luotonins, quinoline alkaloids.⁶

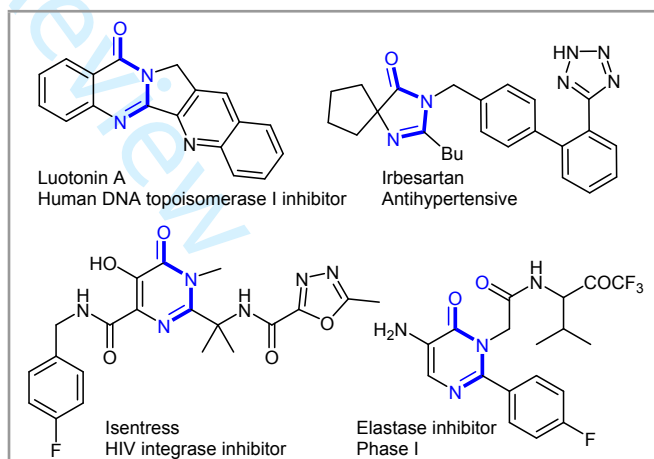


Figure 1 Pharmaceutical molecules and biomolecules incorporating a 1,3-diazol-4-one core

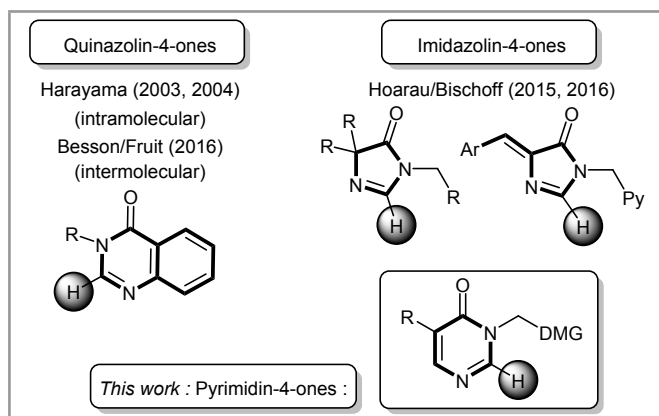
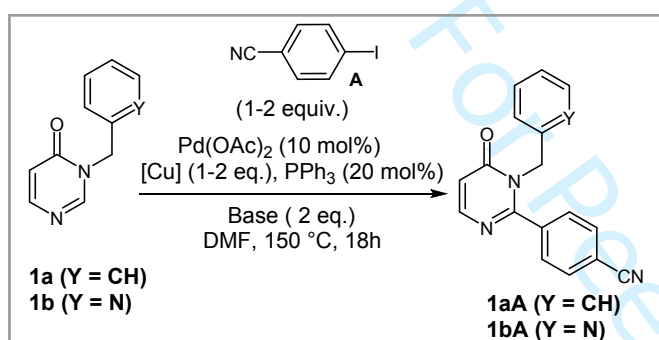


Figure 2 Direct C(2)-H functionalization of 1,3-diazol-4-ones heterocycles: Pioneer investigations in quinazolin-4-one and imidazole-4-ones and presently in pyrimidin-4-one.



Scheme 1 Direct C-H arylation of *N*-benzyl and *N*-picolinyl pyrimidinones under various catalysis^a

Table 1 Optimization of experimental conditions

Entry	Y	[Cu]/ArX	Base	T°C	Yield ^b [%]
1 ^c	CH	-	KOAc	130	n.r.
2 ^c	CH	-	K ₂ CO ₃	130	n.r.
3	CH	CuBr.Me ₂ S (1:1)	DBU	130	14
4	N	CuBr.Me ₂ S (1:1)	DBU	130	54
5	N	CuBr.Me ₂ S (1:1)	CsF	130	52
6	N	CuBr.Me ₂ S (1:1)	K ₃ PO ₄	130	29
7	N	CuBr.Me ₂ S (1:2)	DBU	130	63
8	N	CuBr.Me ₂ S (2:2)	CsF	130	54
9	N	CuI (2:2)	DBU	150	48
10	N	CuBr.Me ₂ S (2:2)	DBU	150	56
11	N	CuI (2:2)	CsF	150	74 ^d

^aReaction conditions: [Pd] (5 mol%), ligand (10 mol%), **1a** (0.5 mmol), base (2 equiv), 130°C, 12 h. ^bYield based on isolated product after flash chromatography. ^cPCy₃ ligand and 1 equiv of ArX. ^dOperating on 1.0 mmol of **1a**.

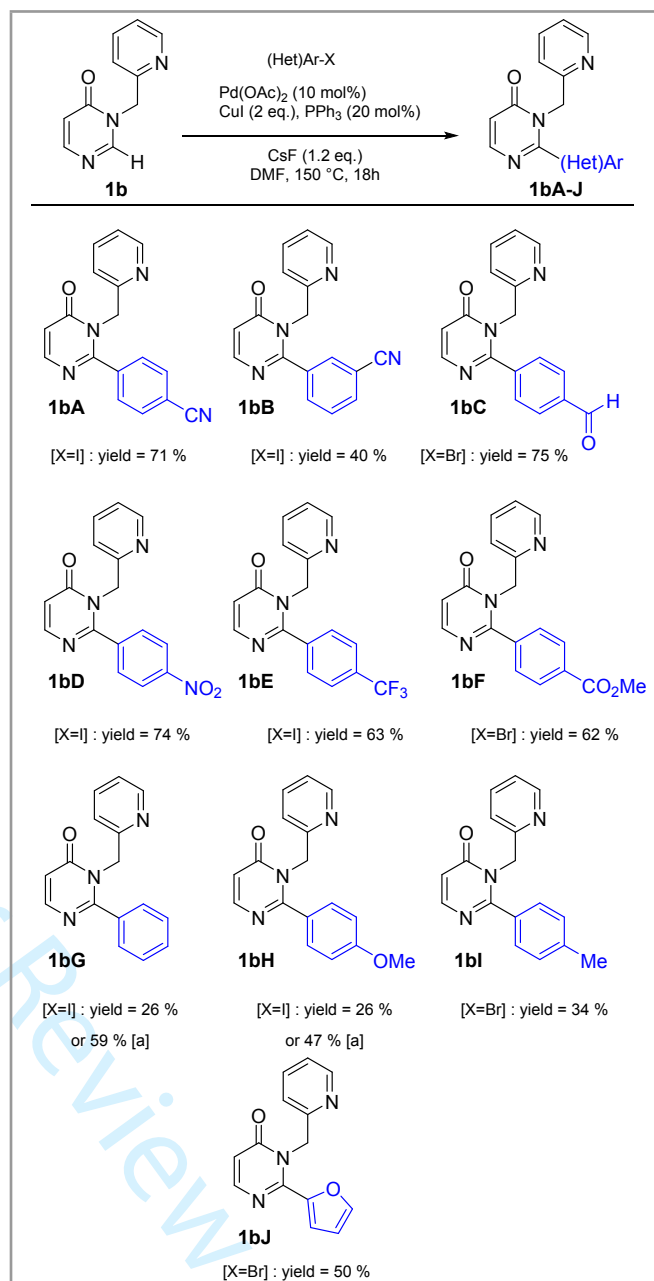
Recently, we first investigated the palladium(0)-catalyzed and copper-assisted direct C(2)-H arylation of 4,4'-dialkyl- and 4-arylidene imidazolones applied to the design of novel GFP-like and Kaede protein fluorophores for bioimaging.^{7,8} The methodology was then proved to be effective in direct C(2)-H heteroarylation of quinazolinone (**Figure 2**).⁹ In our ongoing investigations on challenging 1,3-diazol-4-one non aromatic heterocycles, we turned our investigations to the important class of *N*-substituted pyrimidin-4-ones present in many biologically-active compounds such as HIV integrase inhibitor, elastase.² Herein the ortho-directed direct C(2)-H arylation of various pyrimidin-4-ones with aryl halides is reported under cooperative Pd(0)/Cu(I) catalysis. Two ortho-directing substituents (DMGs) flanked at nitrogen atom have been screened including pyridine and nitrile that is highly chemically-amenable towards several *N*-substitutions for drug design. The subsequent removal of DMG was also explored to produce *N*(3)-H free pyrimidinones. The sequential Suzuki-Miyaura cross-coupling of *N*-substituted 5-bromopyrimidin-4-one followed by direct C(2)-H functionalization with aryl halides to produce disubstituted 2,5-pyrimidin-4-ones was also examined.

A first exploration of palladium-catalyzed direct C-H arylation of the *N*-benzyl pyrimidin-4-one with 4-iodobenzonitrile was achieved under standard catalysis, Pd(OAc)₂ and PPh₃ were used as catalyst/ligand pair. Though a broad screening of bases including acetate and carbonate that found previously operative in intramolecular C(2)-H arylation of quinazolines proposed by Harayama group,⁶ the expected C(2)-arylated pyrimidin-4-one **1aA** was not detected (**Table 1**, entries 1 and 2). To face this difficulty and on the basis of our experience in imidazole-4-one series,^{7,8} we turned immediately to the use of copper(I) salts as additives in combination with DBU base. The C(2)-arylated pyrimidin-4-one **1aA** using CuBr.Me₂S as copper source was isolated albeit in poor 14% yield. We next focused on the picolinyl group (**1b**) as ortho-directing group in direct C-H arylation of azole series,¹⁰ including 4,4'-arylidene imidazolones investigated in our laboratory.⁸ In that case, the yield of the C(2)-H arylation of **1bA** was dramatically increased to 54% under the same catalysis (**Table 1**, entry 4). We observed interestingly that the soft base CsF was identically effective whilst the reaction found less performant using phosphate (**Table 1**, entries 5 and 6). A further examination in details of the influence of copper stoichiometry using two different bases (DBU and CsF) and two sources of copper (CuBr.Me₂S and CuI) at both 130°C and 150°C temperatures led to an optimized catalysis (two-fold excess of electrophile, CuI, CsF (1.2 equivalent) in DMF at 150°C during 18h (**Table 1**, entries 7-11). The 2-arylated *N*-picolinylpyrimidin-4-one **1bA** was thus produced in 74% isolated yield (**Table 1**, entry 11).

The scope of aryl iodides and bromides as electrophiles was then examined under above optimized reaction conditions (**Figure 3**).²⁴ Good performance of C(2)-H arylation of **1b** was observed with aryl bromide or iodide electrophiles substituted by electron-withdrawing groups including chemically-sensitive groups (-CN, -CHO, -NO₂, -CF₃ or -CO₂Me) flanked at the para and meta positions. A first set of C(2)-arylated *N*-picolinylpyrimidin-4-ones (**1bB-1bF**) was prepared in a range of 40 to 75% yields. By contrast the reaction proceeded smoothly with

bromobenzene and other electron-rich aryl halides over 18h reaction time. Interestingly, the yield of phenylated (**1bG**) and 4-methoxyarylated models (**1bH**) could reach fair 59 and 47% values over a longer 42h reaction time. Nevertheless, the *para*-tolyl model (**1bI**) provides a 34% yield for reasons not yet explained. Contrary to our observations in 4-arylidene series,⁸ the 2-bromofuran was identified as one of rare effective coupling partners among diverse halogenated heterocycles (thiophene, pyridine, quinoline) to produce the 2-furanyl model (**1bJ**) in fair yield (50%).

At this stage, the C(2)-H arylation process was evaluated on pyrimidin-4-ones variously substituted at both N(3) and C(5) sites (**Figure 4**). Notably, assuming that the cyano group is highly chemically-amenable towards various functions and substitutions and might act as a coordinating group via dimers,¹¹ the 2-cyanoethyl group was selected as directing group. It was readily introduced at the N(3)-H site through Michael addition reaction of pyrimidin-4-one onto acrylonitrile.¹²



Interestingly, the C(2)-H arylation of *N*-(2-cyanoethyl)pyrimidinone **2** with *para*-cyano and *para*-nitrobenzenes found immediately conclusive applying the optimal protocol to give the C(2)-arylated *N*-(2-cyanoethyl)pyrimidinone **2A-B** in fair 52 and 49% yields (**Figure 4**).

The behavior of the C(2)-H arylation reaction employing C(5)-arylated *N*-picolinyl pyrimidin-4-ones was next studied. To this end, we took advantage of the high C(5)-H electron-density to prepare 5-iodopyrimidinone by treatment of commercially available N(3)-H pyrimidinone with iodine.¹³

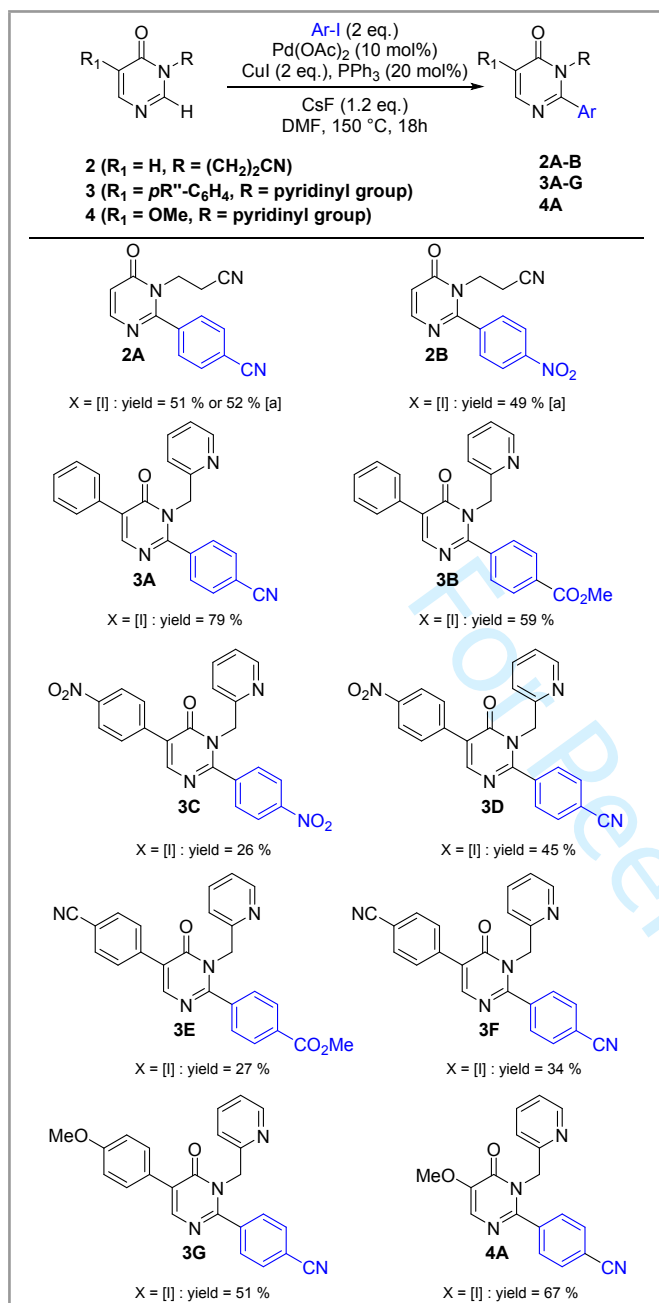
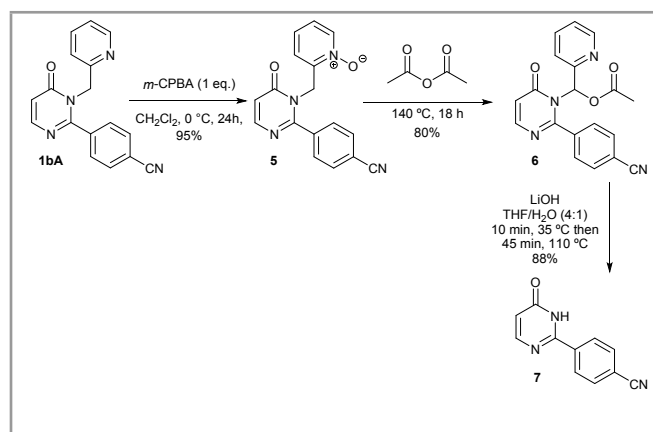


Figure 4 Pd-catalyzed direct C-H arylation of *N*-picolinyl pyrimidinones substituted at C5; [a] Pd(dppf)Cl₂ (10 mol%) was used instead of the mixture Pd(OAc)₂ (10 mol%) and PPh₃ (20 mol%).

A set of 5-arylated *N*-picolinylpyrimidin-4-ones **3** was then prepared in good yields by achieving the picolinyl group introduction at N(3)-H site followed by palladium-catalyzed Suzuki-coupling reactions with various aryl halides⁹ including electron-deficient para-cyano and carboxy iodobenzenes. Applying the previously-optimized protocol for C(2)-H arylation of non-substituted N(3)-picolinyl pyrimidin-4-one with haloarenes, several 2,5-diarylated pyrimidin-4-ones were obtained in a range of 26 to 79 % isolated yields (**Figure 4**). Worth noting, these N(3)-picolinyl 2,5-diaryl pyrimidinones embedded with a push-pull electronic system represent innovative structural analogs of 4-arylidene imidazolone-based GFP Protein Fluorophores.⁸

As last demonstration of the robustness of the protocol, the 5-methoxy pyrimidin-4-one **4**,¹⁰ used as pharmaceutical scaffold in drug-design, was evaluated. Pleasingly and despite the higher electron density of the pyrimidin-4-one ring, the C(2)-H arylation of **1b** with para-cyano iodobenzene as testing reagent was successfully carried out under optimized reaction conditions producing the C(2)-arylated 5-methoxy pyrimidin-4-one **4A** in fair 67% yield.



Scheme 2 Picolinyl cleavage *via* Boekelheide rearrangement

The final investigations (**Scheme 2**) were directed towards evaluation of the 3-step removal of the picolinyl protecting group using Boekelheide rearrangement¹⁵ from *N*-picolinyl C(2)-arylated pyrimidinone **1bA** as selected substrate.¹⁶ As first step, the pyridine moiety was oxidized by treatment with *m*CPBA, providing the pyrimidinone *N*-oxide **5** in 95% yield. The subsequent Boekelheide rearrangement by treatment with acetic anhydride following reported procedures led to the α -acetoxy pyrimidinone **6** in 80% isolated yield. Final treatment with LiOH afforded the N(3)-H free C(2)-arylated pyrimidinone **7** in 67% yield over this 3-step sequence.¹⁷ The removal of 2-cyanoethyl group from nitrogen atom was also envisaged through a base-promoted retro-Michael reaction.¹⁸ Deprotection of 2-cyanoethylpyrimidinone **2A** using nucleophilic bases such as diethylamine and DBU in acetonitrile proceeded only with 20% yield.

The developed palladium-catalyzed C(2)-H arylation of pyrimidin-4-one promoted by N(3)-protecting group, CuI additive and carbonate may involve different C(2)-H metalation-deprotonation pathways. Notably, assuming that Cu^I can bind to N(1)-site reinforcing C(2)-H acidity, several base-assisted metalation-deprotonation models might be postulated involving different key roles of N(3)-protecting group (**Figure 5**). Firstly, supporting by works of Huang,¹⁹ Gorelsky²⁰ and Blagg²¹ groups in (benzo)oxa(thia)zoles, (benzo)imidazole and pyridoimidazole series respectively, an external base-assisted concerted metalation-deprotonation (CMD) might take place through coordination to picolinyl group of aryl halopalladium active complex generated by oxidative addition of Pd(0) to C-X bond (Model A, **Figure 5**). By contrast, inspiring by reports of C(2)-H arylation in imidazole series of Bellina and Rossi²² and then other groups²³, we assume that Ar-Cu complex may be generated, acting as transmetalating agent into a standard Pd(0)-catalyzed cross-coupling cycle namely Pd(0) / Cu^I cooperative catalysis. In that case, two external base-assisted

C(2)-H activation processes might be suggested, (i) first, a concerted cupratation-deprotonation involving Cu^I coordinated to DMG instead of N(1)-site (Model B, **Figure 5**) and, (ii) a carbanionic-type cupratation implying Cu^I bound to N(1)-site while DMG is locked-in via double Cu^I-coordination involving additionally the carbonyl function (Model C).

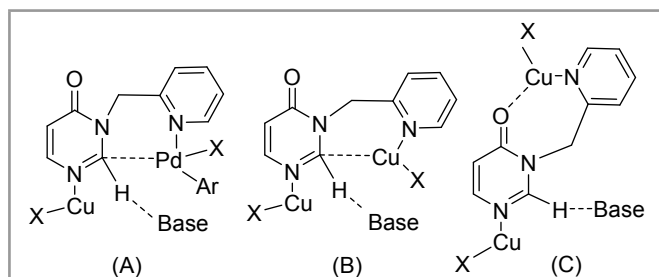


Figure 5 Models of C(2)-H activations of base-assisted Pd(II)-catalyzed C(2)-H arylation of *N*-picolinylpyrimidin-4-one using Cu^I additive.

In summary, we report here the first examples of C(2)-H arylation of pyrimidin-4-ones with aryl halides using picolinyl and 2-cyanoethyl directing groups that may promote the catalytic-metalation key-step along with being removable and/or highly chemically-scalable. The synthetic process tolerates a broad variety of aryl halides as well as the presence of functions sensitive to nucleophilic attack. The 5-arylated pyrimidin-4-ones found also an operative substrate to produce 2,5-diarylated *N*-picolinyl pyrimidin-4-one as innovative structurally-related imidazolone-based GFP protein fluorophores. Additionally, the 5-methoxy pyrimidin-4-one actively used in drug design was also successfully reacted giving access to C(2)-arylated 5-methoxy pyrimidin-4-one. The removal of the picolinyl protecting-group was finally demonstrated through a 3-step oxidation, Boekelheide rearrangement and hydrolysis sequence.

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Supporting Information

YES (this text will be updated with links prior to publication)

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References and Notes

- (1) For reviews on the Pd-catalyzed direct C(sp²)-H arylation of heterocycles (C-H/C-X coupling), see: (a) Verbitskiy, E. V.; Rusinov, G. L.; Chupakhin, O. N.; Charushin, V. N. *Synthesis* **2018**, *50*, 193; (b) Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. *Chem. Rev.*, **2017**, *117*, 9302; (c) Abdoli, M.; Mirjafary, Z.; Saeidian, H.;

Kakanejadifard, A. *RSC Adv.*, **2015**, *5*, 44371; (d) Liang, Y.; Wnuk, S. F. *Molecules*, **2015**, *20*, 4874; (e) Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. *Adv. Synth. Catal.*, **2014**, *356*, 17; (f) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.*, **2012**, *51*, 8960; (g) Zhao, D.; You, J.; Hu, C. *Chem. Eur. J.*, **2011**, *17*, 5466; (h) Ackermann, L.; Vicente, R.; Kapdi, A.R. *Angew. Chem. Int. Ed.*, **2009**, *48*, 9792; (i) Bellina, F.; Rossi, R. *Tetrahedron*, **2009**, *65*, 10269; (j) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.*, **2007**, *107*, 174; (k) Satoh, T.; Miura, M. *Chem. Lett.*, **2007**, *36*, 200; (l) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.*, **2007**, *36*, 1058; (m) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.*, **2007**, *36*, 1173.

- (2) For selected reviews on quinazolin-4-one activities, see: (a) Gatadi, S.; Lakshmi, T. V.; Nanduri, S. *Eur. J. Med. Chem.* **2019**, *170*, 157; (b) Khan, I.; Zaib, S.; Batool, S.; Abbas, N.; Ashraf, Z.; Iqbal, J.; Saeed, A. *Bioorg. Med. Chem.* **2016**, *24*, 2361; (c) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650. For selected articles on pyrimidin-4-one activities, see: (a) Sharma, R.; Gawande, D. Y.; Mohan, C.; Goel, R. K. *Med. Chem. Res.* **2016**, *25*, 1420; (b) Sagong, H. Y.; Bauman, J. D.; Patel, D.; Das, K.; Arnold, E.; LaVoie, E. J. *J. Med. Chem.* **2014**, *57*, 8086; (c) Bellomo, A.; Celebi-Olcum, N.; Bu, X.; Rivera, N.; Ruck, R. T.; Welch, C. J.; Houk, K. N.; Dreher, S. D. *Angew. Chem. Int. Ed.* **2012**, *51*, 6912; (d) Summa, V.; Petrocchi, A.; Matassa, V. G.; Taliani, M.; Laufer, R.; De Francesco, R.; Altamura, S.; Pace, P. *J. Med. Chem.* **2004**, *47*, 5336. For selected articles on imidazol-4-one activities, see: (a) Chen, Y.; O'Connor, S. J.; Guan, D. Newcom, J.; Chen, J.; Yi, L.; Zhang, H.; Hunyadi, L. M.; Natero, R. WO PCT 058727, 2004; (b) Murugesan, N.; Tellev, J. E.; Macor, J. E.; Gu, Z. WO PCT 01389, 2000; (c) Murugesan, N.; Tellev, J. E.; Macor, J. E.; Gu, Z. US PCT0143024, 2002
- (3) For selected reviews on the quinazolin-4-ones synthesis, see: (a) Rohokale, R. S.; Kshirsagar, U. A. *Synthesis* **2016**, *48*, 1253; (b) Maiden, T. M. M.; Harrity, J. P. A. *Org. Biomol. Chem.* **2016**, *14*, 8014; (c) Kshirsagar, U. A. *Org. Biomol. Chem.* **2015**, *13*, 9336; (d) He, L.; Li, H.; Chen, J.; Wu, X.-F. *RSC Adv.* **2014**, *4*, 12065; (e) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153. For selected articles on the pyrimidin-4-ones synthesis, see: (a) Ramanjulu, J. M.; DeMartino, M. P.; Lan, Y.; Marquis, R. *Org. Lett.* **2010**, *12*, 2270; (b) Jeong, J. U.; Chen, X.; Rahman, A.; Yamashita, D.; Luengo, J. I. *Org. Lett.* **2004**, *6*, 1013; (c) Jezewski, A.; Jurczak, J.; Lidert, Z.; Tice, C. M. *J. Heterocycl. Chem.* **2001**, *38*, 645; (d) Takahashi, T.; Hirokami, S.; Nagata, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2653; (e) Salimbeni, A.; Canevotti, R.; Paleari, F.; Poma, D.; Caliar, S.; Fici, F.; Cirillo, R.; Renzetti, A.; Subissi, A.; Belvisi, L.; Bravi, G.; Scolastico, C.; Giachetti, A. *J. Med. Chem.* **1995**, *38*, 4806; (f) Pinner, A. *Chem. Ber.* **1889**, *22*, 1612. For selected articles on imidazol-4-ones synthesis, see: Wu, L.; Burgess, K. *J. Am. Chem. Soc.* **2008**, *130*, 4089; (b) Baranov, M. S.; Solntsev, K. M.; Lukyanov, K. A.; Yampolsky, I. V. *Chem. Commun.* **2013**, *49*, 5778 (c) Baldrige, A.; Samanta, S. R.; Jayaraj, N.; Ramamurthy, V.; Tolbert, L. M. *J. Am. Chem. Soc.* **2011**, *133*, 712
- (4) For reviews on the Liebeskind-Srogl cross-coupling reaction, see: (a) Cheng, H.-G.; Chen, H.; Liu, Y.; Zhou, Q. *Asian J. Org. Chem.*, **2018**, *7*, 490; (b) Prokopcová, H.; Kappe, C. O. *Angew. Chem. Int. Ed.*, **2009**, *48*, 2276
- (5) For the Liebeskind-Srogl cross-coupling reaction at C-2 of quinazolinone, pyrimidinone or imidazolone nucleus, see: (a) Kriščiūnienė, V.; Matulevičiūtė, G.; Paliulis, O.; Rollin, P.; Šačkus, A. *Heterocycles*, **2016**, *93*, 150; (b) Gosling, S.; Rollin, P.; Tatibouët, A. *Synthesis*, **2011**, *22*, 3649; (c) Sun, Q.; Suzenet, F.; Guillaumet, G. *J. Org. Chem.*, **2010**, *75*, 3473; (d) Prokopcová, H.; Pisani, L.; Kappe, C. O. *Synlett*, **2007**, *1*, 43; (e) Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. *Org. Lett.*, **2003**, *5*, 4349; (f) Oumouch, S.; Bourotte, M.; Schmitt, M.; Bourguignon, J.-J. *Synthesis*, **2005**, *1*, 25
- (6) (a) Harayama, T.; Morikami, Y.; Shigeta, Y.; Abe, H.; Takeuchi, Y. *Synlett*, **2003**, *6*, 847-848; (b) Harayama, T.; Hori, A.; Serban, G.; Morikami, Y.; Matsumoto, T.; Abe, H.; Takeuchi, Y. *Tetrahedron* **2004**, *60*, 10645

- (7) Muselli, M.; Baudequin, C.; Hoarau, C.; Bischoff, L. *Chem. Commun.* **2015**, *51*, 745
- (8) Muselli, M.; Baudequin, C.; Perrio, C.; Hoarau, C.; Bischoff, L. *Chem. Eur. J.* **2016**, *22*, 5520.
- (9) Laclef, S.; Harari, M.; Godeau, J.; Schmitz-Afonso, I.; Bischoff, L.; Hoarau, C.; Levacher, V.; Fruit, C.; Besson, T. *Org. Lett.* **2015**, *17*, 1700
- (10) For selected articles using picolinyl and derivatives (picolinamide) group as ortho-directing group, see: Pradhan, S.; De, P. B.; Punniyamurthy, T. *J. Org. Chem.* **2017**, *82*, 4883
- (11) For a recent review, see: Ping, Y.; Wang, L.; Ding, Q.; Peng, Y. *Adv. Synth. Catal.*, **2017**, *359*, 3274
- (12) Arumugam, J.; Brown, H. A.; Jacobs, H. K.; Gopalan, A. S. *Synthesis* **2011**, *1*, 57
- (13) Sakamoto, T.; Kondo, Y.; Watanabe, R.; Yamanaka, H. *Chem. Pharm. Bull.*, **1986**, *34*, 2719
- (14) 5-methoxy pyrimidin-4-one was synthesized according to the literature: Myllymäki, M. J.; Käsnänen, H.; Kataja, A. O.; Lahtela-Kakkonen, M.; Saario, S. M.; Poso, A.; Koskinen, A. M. P. *Eur. J. Med. Chem.*, **2009**, *44*, 4179
- (15) Boekelheide, V.; Linn, W. J. *J. Am. Chem. Soc.*, **1954**, *76*, 1286.
- (16) For deprotection of pyridinyl group involving Boekelheide rearrangement, see: (a) Mizuno, Y.; Endo, T.; Miyaoka, T.; Ikeda, K. *J. Org. Chem.*, **1974**, *39*, 1250; (b) Endo, T.; Ikeda, K.; Kawamura, Y.; Mizuno, Y. *J. C. S. Chem. Comm.*, **1973**, 673
- (17) Andreotti, D.; Miserazzi, E.; Nalin, A.; Pozzan, A.; Profeta, R.; Spada, S. *Tetrahedron Lett.*, **2010**, *51*, 6526
- (18) For selected articles on *N*-ethylcyano deprotection, see: (a) Tolstyakov, V. V. *Chem. Heterocycl. Compd.* **2017**, *53*, 719; (b) Tanino, T.; Yamaguchi, M.; Matsuda, A.; Ichikawa, S. *Eur. J. Org. Chem.*, **2014**, 1836; (c) Touti, F.; Avenier, F.; Lefebvre, Q.; Maurin, P.; Hasserodt, J. *Eur. J. Org. Chem.* **2010**, 1928; (d) Liao, Y.; Robinson, B. H. *Tetrahedron Lett.*; **2004**, *45*, 1473; (e) Duncia, J. V.; Pierce, M. E.; Santella III, J. B. *J. Org. Chem.* **1991**, *56*, 2395.
- (19) Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 3674
- (20) Gorelsky, S. I. *Organometallics* **2012**, *31*, 794
- (21) Macdonald, J.; Oldfield, V.; Bavetsias, V.; Blagg, J. *Org. Biomol. Chem.* **2013**, *11*, 2335
- (22) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *Eur. J. Org. Chem.* **2006**, 693
- (23) (a) Lesieur, M.; Lazreg, F.; Cazin, C. S. J. *Chem. Commun.* **2014**, *50*, 8927; (b) Storr, T. E.; Baumann, C. G.; Thatcher, R. J.; De Ornellas, S.; Whitwood, A. C.; Fairlamb, I. J. S. *J. Org. Chem.* **2009**, *74*, 5810; (c) Storr, T. E.; Firth, A. G.; Wilson, K.; Darley, K.; Baumann, C. G.; Fairlamb, I. J. S. *Tetrahedron* **2008**, *64*, 6125
- (24) *N*-alkylated pyrimidin-4-one (0.5 mmol) was placed in an oven-dried screw-capped sealed tube (10 mL) containing a magnetic stir bar with Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%), CuI (2 eq.) and CsF (1,2 eq.). A solution of halide (2 eq.) in DMF (1.5 mL) was added. The resulting mixture was purged with nitrogen and stirred at 150 °C for 18 h. After dilution with DCM, filtration on cotton, washing with 5% aqueous ammonia (2x25 mL), brine (2x25 mL), drying over anhydrous Na₂SO₄ and concentration in vacuo, the crude product was purified by flash column chromatography through silica gel using a mixture of appropriate solvents as eluent to give pure arylated product.

Supporting information section for:

Ortho-directed Palladium-catalyzed Direct C-H Functionalization of *N*-picolinyl and 2-cyanoethyl Pyrimidinones with Aryl Halides

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1. General information

1.1 Solvents and reagents

All commercially available reagents were purchased from Sigma/Aldrich, Alfa Aesar, ACROS or TCI Europe and used without further purification. Solvents were dried through solvent purification system "Pure Solv MD 5" and stored under argon. Copper iodide was purified following reported procedure.¹ Triphenylphosphine was recrystallized from ethanol.

1.2 Chromatography

All reactions were monitored by thin-layer chromatography using Merck silica gel 60 F254 pre-coated aluminum plates (0.25 mm) under UV light (254 nm) and/or by the use of ethanolic vanillin or aqueous potassium permanganate. Flash chromatography was performed with indicated solvents using silica gel (particle size 30–63 μm) purchased from Merck.

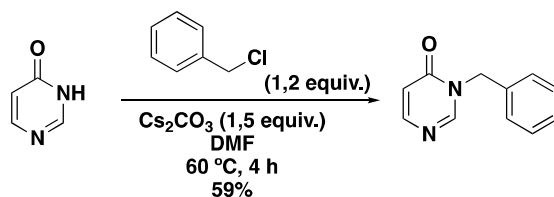
1.3 Instruments

¹H and ¹³C NMR spectra were recorded at room temperature on a Bruker Advance spectrometer operating at 300 MHz for ¹H and 75 MHz for ¹³C using the solvent signal as an internal standard. Chemical shifts are reported in parts per million (ppm). Coupling constants (J) are given in Hertz (Hz). The following abbreviations are used for the proton spectra multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). HR-MS analyses were performed with a Waters LCT U Premier XE (ESI).

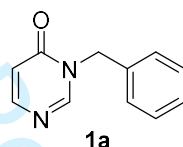
¹ R. K. Dieter, L. A. Silks III, J. R. Fishpugh, M. E. Kastner, *J. Am. Chem. Soc.* **1985**, 107, 4679-4692.

2. Synthesis of the *N*-alkylated of 4(3*H*)-pyrimidinone.

a. Synthesis of the 3-benzylpyrimidin-4(3*H*)-one **1aA**



To a stirred mixture of pyrimidin-4(3*H*)-one (2 g, 20.8 mmol) and benzyl chloride (3.2 g, 25 mmol) in DMF (250 mL), cesium carbonate (10.2 g, 31.2 mmol) was added at room temperature. The mixture was heated at 60 °C for 4 h (monitored by TLC). Then, the mixture was filtered through a short pad of Celite®, washed with EtOAc and the solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography, using CH₂Cl₂ (100%) to afford the title compound in 59% yield as a white solid (2.27 g, 12.2 mmol).



Aspect: white solid²

Mp = 105 – 107 °C (CH₂Cl₂/PE)

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.06 (s, 1H, C2-H), 7.77 (d, *J* = 6.5 Hz, 1H, C6-H), 7.27-7.20 (m, 5H, CH_{benz}), 6.37 (d, *J* = 6.6 Hz, 1H, C5-H), 5.00 (s, 2H, CH₂).

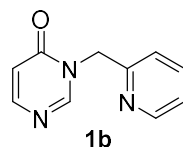
¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 160.8 (C=O), 153.2 (CH), 151.1 (CH), 135.0 (Cq), 129.0 (CH×2), 128.4 (CH), 128.1 (CH×2), 116.1 (CH), 49.6 (CH₂).

IR (ATR, cm⁻¹): 3057, 3005, 2957, 1665, 834, 735, 696, 542, 501 cm⁻¹.

HRMS (ESI-TOF) *m/z*: Anal. Calcd for C₁₁H₁₁N₂O: [M+H]⁺ 187.0871, found 187.0871.

b. Synthesis of the 3-(pyridin-2-ylmethyl)pyrimidin-4(3*H*)-one **1b**

To a stirred mixture of pyrimidin-4(3*H*)-one (2.75 g, 28.6 mmol) and 2-(chloromethyl)pyridine hydrochloride (5.63 g, 34.3 mmol) in DMF (300 mL), cesium carbonate (23.31 g, 71.5 mmol) was added at room temperature. The mixture was heated at 60 °C for 4 h (monitored by TLC). Then, the mixture was filtered through a short pad of Celite®, washed with EtOAc and the solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography, using AcOEt (100%) to afford the title compound in 75% yield as a pale yellow solid (4.04 g, 21.6 mmol).



Aspect: yellow solid

Mp: 124 – 126 °C (CH₂Cl₂/Pentane)

² S. M. Roopan, F. R. N. Khan, B. K. Mandal, *Tet. Lett.*, **2010**, *51*, 2309-2311.

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.46 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H, CH_{pyr}), 8.32 (s, 1H, C2-H), 7.80 (d, J = 6.6 Hz, 1H, C6-H), 7.59 (td, J = 7.7, 1.8 Hz, 1H, CH_{pyr}), 7.32 (d, J = 7.8 Hz, 1H, CH_{pyr}), 7.14 (ddd, J = 7.6, 4.9, 1.1 Hz, 1H, CH_{pyr}), 6.36 (dd, J = 6.6, 0.9 Hz, 1H, C5-H), 5.10 (s, 2H, N-CH₂).

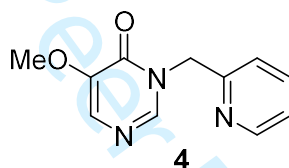
¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 160.6 (Cq, C=O), 154.1 (Cq_{pyr}), 153.4 (C6-H), 151.9 (C2-H), 149.6 (CH_{pyr}), 136.9 (CH_{pyr}), 123.1 (CH_{pyr}), 123.0 (CH_{pyr}), 115.8 (C5-H), 51.0 (N-CH₂).

IR (ATR, cm⁻¹): 3052, 3004, 2946, 1658, 1569, 1532, 1435, 1425, 1373, 853, 755, 546, 503 cm⁻¹.

HRMS (ESI-TOF) m/z : Anal. Calcd for C₁₀H₁₀N₃O: [M+H]⁺ 188.0824, found 188.0822.

c. Synthesis of the 5-methoxy-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one **4**

5-methoxypyrimidin-4(3H)-one (1g, 7.08 mmol), 2-(chloromethyl)pyridine hydrochloride (1.40g, 8.5 mmol) was introduced to a solution of cesium carbonate (5.77g, 17.71mmol) in DMF (65mL) at room temperature. The reaction mixture was stirred at 60°C for 4h. Then, the mixture was filtered through a Celite® pad and concentrated under vacuo. The product was purified by silica gel column chromatography, using CH₂Cl₂ (100%), CH₂Cl₂/EtOAc (50:50) and EtOAc (100%) as eluent to afford the title compound in 72 % yield as a white solid (1.18g).



Aspect: white solid

Mp = 108 – 112 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ (ppm) = 8.52 (d, J = 4.8 Hz, 1H, CH_{pyr}), 8.07 (s, 1H, C2-H), 7.66 (td, J = 7.7, 1.8 Hz, 1H, CH_{pyr}), 7.42 (d, J = 7.9 Hz, 1H, CH_{pyr}), 7.40 (s, 1H, C6-H), 7.21 (ddd, J = 7.6, 4.9, 0.9 Hz, 1H, CH_{pyr}), 5.21 (s, 2H, N-CH₂), 3.82 (s, 3H, OCH₃).

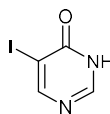
¹³C NMR (CDCl₃, 75 MHz): δ (ppm) = 157.3 (Cq), 154.4 (Cq), 149.8 (CH_{pyr}), 147.3 (Cq, C5), 143.5 (C2-H), 137.1 (CH_{pyr}), 128.7 (CH), 123.5 (CH_{pyr}), 123.3 (CH_{pyr}), 56.4 (OCH₃), 51.2 (N-CH₂).

IR (ATR, cm⁻¹): 3043, 2933, 2843, 1680, 1599, 1269, 770, 594 cm⁻¹.

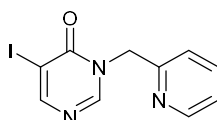
HRMS (ESI-TOF) m/z : Calcd for C₁₁H₁₂N₃O₂: [M+H]⁺ 218.0930, found 218.0930.

3. Suzuki-Miyaura cross-coupling reaction

a. Synthesis of starting materials



5-iodopyrimidin-4(3H)-one: Pyrimidin-4(3H)-one (2 g, 20.8 mmol), I₂ (5.30 g, 20.8 mmol) and NaOH (1.1 g, 27.8 mmol) were introduced in 21 mL of water. Then the mixture was stirred at 80°C during 20 h. The solution was neutralized with AcOH and the precipitate was recrystallized from acetone to give 5-iodopyrimidin-4(3H)-one (1.63 g, 7.3 mmol) as a white solid. Yield = 53%. This is a known compound and the spectral data are identical to those reported in literature.³



5-iodo-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one : To a stirred mixture of 5-iodopyrimidin-4(3H)-one (1.31 g, 5.9 mmol) and 2-(chloromethyl)pyridine hydrochloride (1 g, 6.1 mmol) in DMF (50 mL), cesium carbonate (4.15 g, 12.7 mmol) was added at room temperature. The mixture was heated at 60 °C for 7 h (monitored by TLC). Then, the mixture was filtered through a short pad of Celite®, washed with EtOAc and the solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography, using AcOEt/acetone (8/2) to afford the title compound in 75% yield as a white solid (1.19 g, 3.8 mmol).

Aspect: white solid

Mp: 148 °C (EtOH/EP)

¹H NMR (CDCl₃, 300 MHz): δ = 8.53 (d, *J* = 4.8 Hz, 1H, CH_{pyr}), 8.38 (s, 1H), 8.37 (s, 1H), 7.69 (td, *J* = 7.7, 1.8 Hz, 1H, CH_{pyr}), 7.47 (d, *J* = 7.8 Hz, 1H, CH_{pyr}), 7.26-7.22 (m, 1H), 5.19 (s, 2H, N-CH₂).

¹³C NMR (CDCl₃, 75MHz): δ = 160.2 (CH), 158.5 (C=O), 153.4 (C_q_{pyr}), 151.7 (CH), 149.8 (CH_{pyr}), 137.3 (CH_{pyr}), 124.0 (CH_{pyr}), 123.6 (CH_{pyr}), 90.0 (C_q, Cl), 52.7 (N-CH₂).

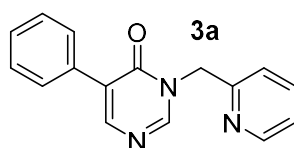
IR (ATR, cm⁻¹): 3043, 1660, 1585, 1384, 1067, 759, 663, 572 cm⁻¹.

HRMS (ESI-TOF) *m/z*: calcd for C₁₀H₉IN₃O:[M+H]⁺ 313.9790; found 313.9795.

a. General procedure B : Suzuki-Miyaura cross-coupling reaction

General procedure A: 5-iodo-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one (1 eq) was placed in an over-dried screw-caped sealed tube (10 ml) containing a magnetic stir bar with Pd(OAc)₂ (5 mol%), PPh₃ (10 mol%), CsF (4 eq) and the boronic acid (2.2 eq) in DMF (C = 0.3 M). The resulting mixture was purged with nitrogen and stirred at 80°C during 5 h. After dilution with AcOEt, washing with brine (3x15mL), drying over anhydrous MgSO₄ and concentration in vacuo, the crude product was purified by flash column chromatography through silica gel using a mixture of appropriate solvents as eluent to give pure arylated product.

³ O. R. Wauchope, M. Velasquez, K. Seley-Radtke, *Synthesis* **2012**, *44*, 3496-3504.



5-phenyl-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one 3a: the compound was prepared according to the general procedure A with phenylboronic acid. The crude product was purified by flash chromatography (AcOEt/Acetone: 8/2) to afford the title compound in 65% yield (165.6 mg, 0.63 mmol) as a white solid.

Aspect: white solid

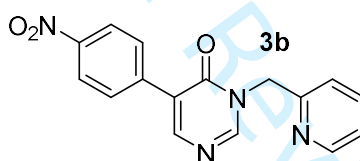
Mp: 124-125 °C (CH₂Cl₂/PE)

¹H NMR (CDCl₃, 300 MHz): δ = 8.56 (d, *J* = 4.5 Hz, 1H, CH_{pyr}), 8.45 (s, 1H), 8.07 (s, 1H), 7.70 (td, *J* = 7.7, 1.6 Hz, 1H, CH_{pyr}), 7.65–7.62 (m, 2H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.43–7.34 (m, 3H), 7.27–7.23 (m, 1H), 5.26 (s, 2H, N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 160.2 (C=O), 154.2 (C_{qpyr}), 154.2 (CH), 150.9 (CH), 150.7 (CH), 149.8 (CH), 137.2 (CH), 133.0 (C_q), 128.5 (2×CH_{arom}), 128.5 (CH), 128.4 (2×CH_{arom}), 127.8 (C_q), 123.7 (CH), 123.3 (CH), 51.8 (N-CH₂)

IR (ATR, cm⁻¹): 3028, 1648, 1388, 1193, 792, 760, 697, 579, 546, 404 cm⁻¹.

HRMS (ESI-TOF) *m/z*: calcd for C₁₆H₁₄N₃O: $[M+H]^+$ 264.1137; found 264.1141.



5-(4-nitrophenyl)-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one 3b : the compound was prepared according to the general procedure A with 4-nitrophenylboronic acid. The crude product was purified by flash chromatography (AcOEt) to afford the title compound in 45% yield (259.4 mg, 0.84 mmol) as a pale-yellow solid.

Aspect: pale yellow solid

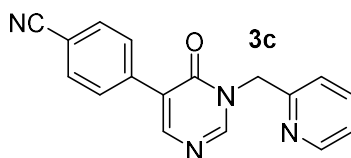
Mp: 191 – 194 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.57–8.55 (m, 1H_{pyr}), 8.51 (s, 1H, C2-H), 8.25 (d, *J* = 9.0 Hz, 2H_{arom}), 8.17 (s, 1H, C6-H), 7.86 (d, *J* = 9.0 Hz, 2H_{arom}), 7.71 (td, *J* = 7.7, 1.8 Hz, 1H_{pyr}), 7.48 (d, *J* = 7.8 Hz, 1H_{pyr}), 7.27–7.23 (m, 1H_{pyr}), 5.25 (s, 2H, N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 159.7 (C=O), 153.7 (C_{qpyr}), 152.3 (CH), 152.1 (CH), 150.0 (CH_{pyr}), 147.6 (C_q-NO₂), 139.8 (C_{qarom}), 137.2 (CH_{pyr}), 129.3 (2×CH_{arom}), 125.7 (C5-q), 123.7 (2×CH_{arom}, 1CH_{pyr}), 123.5 (CH_{pyr}), 51.9 (N-CH₂).

IR (ATR, cm⁻¹): 3101, 3069, 1655, 1506, 1338, 862, 762, 694, 581, 543, 455 cm⁻¹.

HRMS (ESI-TOF) *m/z*: calcd for C₁₆H₁₃N₄O₃: $[M+H]^+$ 309.0988; found 309.9999.



4-(6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-5-yl)benzonitrile 3c : the compound was prepared according to the general procedure A with 4-cyanophenylboronic acid. The crude product was purified by flash chromatography (AcOEt) to afford the title compound in 79% yield (146 mg, 0.51 mmol) as a white solid.

Aspect: white solid

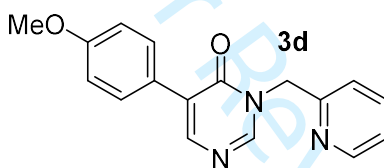
Mp: 167 – 169 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.54 (d, *J* = 4.3 Hz, 1H, CH_{pyr}), 8.49 (s, 1H), 8.11 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 2H, 2×CH_{arom}), 7.71-7.65 (m, 3H, 1 CH_{pyr}, 2×CH_{arom}), 7.46 (d, *J* = 7.8 Hz, 1H, CH_{pyr}), 7.26-7.21 (m, 1H, CH_{pyr}), 5.23 (s, 2H, N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 159.7 (C=O), 153.7 (CH), 151.9 (CH), 149.9 (CH), 137.8 (Cq), 137.2 (CH_{pyr}), 132.1 (2×CH_{arom}), 129.14 (2×CH_{arom}), 125.9 (Cq), 123.6 (CH_{pyr}), 123.5 (CH_{pyr}), 118.7 (Cq), 111.9 (Cq), 51.9 (N-CH₂).

IR (ATR, cm⁻¹): 2222, 1658, 1589, 1524, 1195, 847, 847, 759, 583, 514, 443 cm⁻¹.

HRMS (ESI-TOF) *m/z*: calcd for C₁₇H₁₃N₄O:[M+H]⁺ 289.1089; found 289.1082.



5-(4-methoxyphenyl)-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one 3d : this compound was prepared according to the general procedure A with 4-methoxyphenylboronic acid. The crude product was purified by flash chromatography (AcOEt/Acetone: 8/2) to afford the title compound in 66% yield (305.6 mg, 1.04 mmol) as a white solid.

Aspect: white solid

Mp: 136-137 °C (CH₂Cl₂/EP)

¹H NMR (CDCl₃, 300 MHz): δ = 8.53 (d, *J* = 3.7 Hz, 1H, CH_{pyr}), 8.38 (s, 1H, C2-H), 8.02 (s, 1H, C6-H), 7.66 (td, *J* = 7.7, 1.6 Hz, 1H, CH_{pyr}), 7.59 (d, *J* = 8.8 Hz, 2H, 2×CH_{arom}), 7.46 (d, *J* = 7.7 Hz, 1H, CH_{pyr}), 7.21 (dd, *J* = 7.0, 5.2 Hz, 1H, CH_{pyr}), 6.92 (d, *J* = 8.8 Hz, 2H, 2×CH_{arom}), 5.22 (s, 2H, N-CH₂), 3.80 (s, 3H, OCH₃).

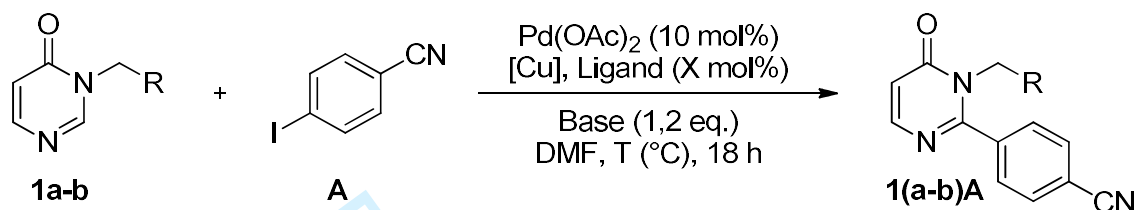
¹³C NMR (CDCl₃, 75MHz): δ = 160.3 (Cq), 159.8 (Cq), 154.3 (Cq), 150.18 (CH), 150.0 (CH), 149.7 (CH), 137.1 (CH_{pyr}), 129.7 (2×CH_{arom}), 125.4 (Cq), 123.6 (CH_{pyr}), 123.3 (CH_{pyr}), 113.9 (2×CH_{arom}), 55.4 (OCH₃), 51.8 (N-CH₂).

IR (ATR, cm⁻¹): 3012.7, 2840.5, 1647.01, 1247.12, 1174.25, 1030.77, 834.94, 759.04, 581.37, 567.04, 546.66 cm⁻¹.

HRMS (ESI-TOF) m/z : calcd for $C_{17}H_{14}N_3O_2$: $[M+H]^+$ 294.1243; found 294.1246.

4. Palladium-Copper-catalyzed direct intermolecular arylation of the C2-H bond

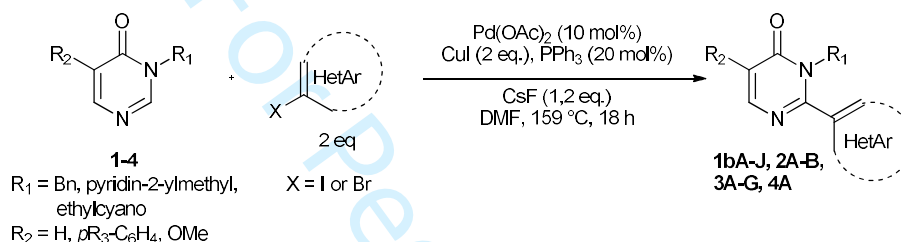
a. Optimization of the intermolecular direct C2-H arylation of *N*-alkylated pyrimidin-4-one.



Entry	R	[Cu]/1A	Ligand (X mol%)	Base (1.2 eq)	T (°C)	Yield (%)
1	Ph	CuBr•DMS (1/1)	PPh ₃ (20 mol%)	DBU	130	14
2	Ph	CuBr•DMS (1/1)	-	DBU	130	8
3	Ph	CuI (1/1)	PPh ₃ (20 mol%)	CsF	130	20
4	Ph	CuI (1/1)	Phenantroline (20 mol%)	CsF	130	35
5	Ph	CuI (1/1)	PPh ₃ (20 mol%)	CsF	150	17
6	Py	CuBr•DMS (1/1)	PPh ₃ (20 mol%)	Cs ₂ CO ₃	130	0
7	Py	CuBr•DMS (1/1)	PPh ₃ (20 mol%)	K ₃ PO ₄	130	0
8	Py	CuBr•DMS (1/1)	PPh ₃ (20 mol%)	DBU	130	54
9	Py	CuBr•DMS (1/1)	PPh ₃ (20 mol%)	CsF	130	52
10	Py	CuI (1/1)	PPh ₃ (20 mol%)	CsF	130	50
11	Py	CuBr•DMS (1/2)	PPh ₃ (20 mol%)	DBU	130	63
12	Py	CuBr•DMS (1/2)	PPh ₃ (20 mol%)	DBU	150	58
13	Py	CuI	PPh ₃	CsF	150	74

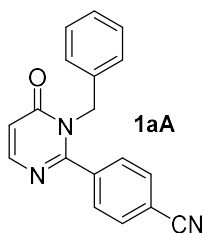
		(1/2)	(20 mol%)			
14	Py	CuI (2/2)	PPh ₃ (20 mol%)	CsF	150	74
15	Py	CuI (2/2)	PPh ₃ (10 mol%)	CsF	150	44
16	Py	CuI (2/2)	-	CsF	150	7
17	Py	CuI (2/2)	Phenantroline (20 mol%)	CsF	150	35
18	Py	- (0/2)	PPh ₃ (20 mol%)	CsF	150	0

b. General procedure C : Palladium-Copper-Catalyzed direct intermolecular arylation of the C2-H bond on *N*-alkylated pyrimidin-4-ones



General procedure B: *N*-alkylated pyrimidin-4-one (0.5 mmol) was placed in an oven-dried screw-capped sealed tube (10 mL) containing a magnetic stir bar with Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%), CuI (2 eq.) and CsF (1,2 eq.). A solution of halide (2 eq.) in DMF (1.5 mL) was added. The resulting mixture was purged with nitrogen and stirred at 150 °C for 18 h. After dilution with DCM, filtration through cotton, washing with 5% aqueous ammonia (2x25 mL), brine (2x25 mL), drying over anhydrous Na₂SO₄ and concentration in vacuo, the crude product was purified by flash column chromatography through silica gel using a mixture of appropriate solvents as eluent to give pure arylated product.

General procedure C: *N*-alkylated pyrimidin-4-one (0.5 mmol) was placed in an oven-dried screw-capped sealed tube (10 mL) containing a magnetic stir bar with Pd(dppf)Cl₂ (10 mol%), CuI (2 eq.) and CsF (1,2 eq.). A solution of halide (2 eq.) in DMF (1.5 mL) was added. The resulting mixture was purged with nitrogen and stirred at 150 °C for 18 h. After dilution with DCM, filtration on cotton, washing with 5% aqueous ammonia (2x25 mL), brine (2x25 mL), drying over anhydrous Na₂SO₄ and concentration in vacuo, the crude product was purified by flash column chromatography through silica gel using a mixture of appropriate solvents as eluent to give pure arylated product.



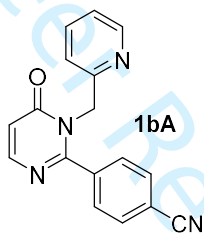
4-(1-benzyl-6-oxo-1,6-dihydropyrimidin-2-yl)benzonitrile 1aA: This compound was prepared according to the general procedure B with 4-iodobenzonitrile (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 20% yield as a pale-yellow solid.

¹H NMR (CDCl₃, 300 MHz): δ = 7.99 (d, J = 6.6 Hz, 1H, C6-H), 7.66 (d, J = 8.6 Hz, 2H, 2×CH_{arom}), 7.36 (d, J = 8.6 Hz, 2H, 2×CH_{arom}), 7.26-7.24 (m, 3H), 6.88-6.85 (m, 2H), 6.60 (d, J = 6.6 Hz, 1H, C5-H), 5.18 (N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 161.8 (Cq), 159.7 (Cq), 152.3 (CH), 138.5 (Cq), 135.5 (Cq), 135.5 (2×CH), 128.9 (2×CH), 128.7 (2×CH), 127.9 (CH), 126.6 (2×CH), 117.8 (Cq), 115.0 (CH), 114.2 (Cq), 48.7 (N-CH₂).

IR (ATR, cm⁻¹): 2970, 2922, 2230, 1674, 1498, 835, 730 cm⁻¹.

HRMS (ESI-TOF) m/z : Anal. Calcd for C₁₈H₁₄N₃O: [M+H]⁺ 288.11369, found 288.11253.



4-(6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-2-yl)benzonitrile 1bA: This compound was prepared according to the general procedure B with 4-iodobenzonitrile (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 74% yield as a brown solid.

Aspect: brown solid

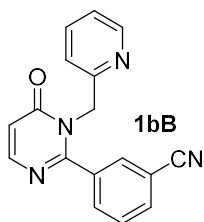
Mp: 98 – 100 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.50 (ddd, J = 4.8, 1.6, 0.9 Hz, 1H_{pyr}), 8.01 (d, J = 6.6 Hz, C6-H), 7.72-7.62 (m, 4H_{arom}, 1H_{pyr}), 7.22-7.19 (m, 2H_{pyr}), 6.53 (d, J = 6.6 Hz, C5-H), 5.16 (s, N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 161.2 (Cq), 159.8 (Cq), 154.2 (Cq), 152.1 (CH), 149.2 (CH), 138.6 (Cq), 136.5 (CH), 132.0 (2×CH_{arom}), 128.8 (2×CH_{arom}), 122.4 (CH), 121.8 (CH), 117.7 (Cq), 114.5 (CH), 113.7 (Cq), 50.3 (N-CH₂).

IR (ATR, cm⁻¹): 3070, 2922, 2852, 2236, 1674, 1497, 1179, 838, 757, 555 cm⁻¹.

HRMS (ESI-TOF) m/z : Anal. Calcd for C₁₇H₁₃N₄O: [M+H]⁺ 289.1089, found 289.1093.



3-(6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-2-yl)benzonitrile 1bB: This compound was prepared according to the general procedure B with 3-iodobenzonitrile (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 63% yield as a brown solid.

Aspect: brown solid

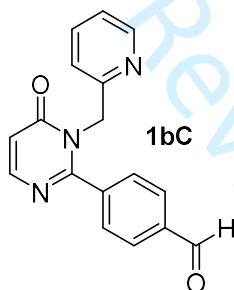
Mp: 93 – 94 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.48 (d, *J* = 4.5 Hz, 1H_{pyr}), 7.97 (d, *J* = 6.6 Hz, 1H, C6-H), 7.86 (td, *J* = 1.7, 0.5 Hz, 1H_{arom}), 7.80 (ddd, *J* = 7.8, 1.7, 1.2 Hz, 1H_{arom}), 7.70 (dt, *J* = 7.8, 1.4 Hz, 1H_{arom}), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H_{pyr}), 7.49 (td, *J* = 7.8, 0.5 Hz, 1H_{arom}), 7.19-7.15 (m, 2H_{pyr}), 6.49 (d, *J* = 6.6 Hz, 1H, C5-H), 5.14 (s, 2H, N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 161.5 (C=O), 159.6 (C_q, C2), 154.4 (C_q_{pyr}), 152.3 (C6-H), 149.5 (CH_{pyr}), 136.8 (CH_{pyr}), 136.0 (C_q), 133.5 (CH), 132.3 (CH), 132.1 (CH), 129.4 (CH_{arom}), 122.8 (CH_{pyr}), 122.2 (CH_{pyr}), 117.7 (C_q), 114.8 (C5-H), 112.9 (C_q), 50.6 (N-CH₂).

IR (ATR, cm⁻¹): 3060, 2236, 1672, 1522, 1165, 809 cm⁻¹.

HRMS (ESI-TOF) *m/z*: Anal. Calcd for C₁₇H₁₃N₄O: [M+H]⁺ 289.1089, found 289.1079.



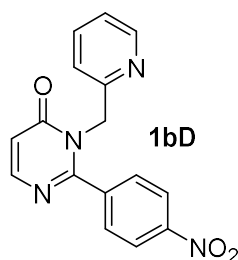
4-(6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-2-yl)benzaldehyde 1bC: This compound was prepared according to the general procedure B with 4-bromobenzaldehyde (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 62% yield as a brown oil.

¹H NMR (CDCl₃, 300 MHz): δ = 10.01 (s, 1H, CHO), 8.48 (d, *J* = 4.5 Hz, 1H, CH_{pyr}), 8.01 (d, *J* = 6.6 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 2H, 2×CH_{arom}), 7.68 (d, *J* = 8.2 Hz, 2H, 2×CH_{arom}), 7.61 (td, *J* = 7.7, 1.7 Hz, 1H, CH_{pyr}), 7.17 (dd, *J* = 7.1, 5.2 Hz, 1H, CH_{pyr}), 7.12 (d, *J* = 7.9 Hz, 1H, CH_{pyr}), 6.52 (d, *J* = 6.6 Hz, 1H), 5.18 (s, 2H, N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 191.4, 161.7, 160.7, 154.6, 152.5, 149.5, 140.0, 137.1, 136.8, 129.7, 128.9, 122.7, 121.9, 114.7, 50.6 (N-CH₂).

IR (ATR, cm⁻¹): 3058, 2922, 2853, 1680, 1516, 1432, 1262, 832, 749, 592 cm⁻¹.

HRMS (ESI-TOF) *m/z*: Anal. Calcd for C₁₇H₁₄N₃O₂: [M+H]⁺ 292.1086, found 292.1092.



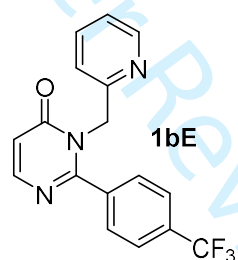
2-(4-nitrophenyl)-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one 1bD: This compound was prepared according to the general procedure B with 1-iodo-4-nitrobenzene (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 71% yield as a brown oil.

^1H NMR (CDCl₃, 300 MHz): δ = 8.51 (dt, J = 4.8, 1.3 Hz, 1H, CH_{pyr}), 8.25 (d, J = 8.9 Hz, 2H, 2×CH_{arom}), 8.02 (d, J = 6.6 Hz, 1H, C6-H), 7.79 (d, J = 8.9 Hz, 2H, 2×CH_{arom}), 7.65 (td, J = 7.7, 1.8 Hz, 1H, CH_{pyr}), 7.22-7.18 (m, 2H, CH_{pyr}), 6.54 (d, J = 6.6 Hz, 1H, C5-H), 5.17 (s, 2H, N-CH₂).

^{13}C NMR (CDCl₃, 75 MHz): δ = 161.5 (Cq), 159.8 (Cq), 154.4(Cq), 152.4 (C6-H), 149.5 (CH_{pyr}), 148.7 (Cq), 140.6 (Cq), 136.9 (CH_{pyr}), 129.6 (2×CH_{arom}), 123.7 (2×CH_{arom}), 122.8 (CH_{pyr}), 122.2 (CH_{pyr}), 115.0 (C5-H), 50.6 (N-CH₂).

IR (ATR, cm⁻¹): 3049, 1674, 1506, 1349, 755, 702 cm⁻¹.

HRMS (ESI-TOF) m/z : Anal. Calcd for C₁₆H₁₂N₄O₃: [M+H]⁺ 309.0984, found 309.0988.



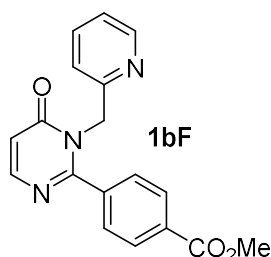
3-(pyridin-2-ylmethyl)-2-(4-(trifluoromethyl)phenyl)pyrimidin-4(3H)-one 1bE: This compound was prepared according to the general procedure B with 4-iodobenzotrifluoride (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 40% yield as a brown oil. **Aspect:** brown oil

^1H NMR (CDCl₃, 300 MHz): δ = 8.49 (s, 1H_{pyr}), 8.00 (d, J = 6.2 Hz, 1H, C6-H), 7.68-7.59 (m, 5H), 7.19-7.13 (m, 2H), 6.51 (d, J = 6.4 Hz, 1H, C5-H), 5.17 (s, 2H, N-CH₂).

^{13}C NMR (CDCl₃, 75 MHz): δ = 161.7 (Cq), 160.6 (Cq), 154.7 (Cq), 152.5 (C6-H), 149.5 (CH_{pyr}), 138.2 (Cq), 136.7 (CH), 132.24 (Cq, q, J = 32.8 Hz), 128.7 (CH_{arom}), 125.64 (CH_{arom}, q, J = 3.7 Hz), 123.6 (Cq, q, J = 270.7 Hz), 114.7 (C5-H), 50.7 (N-CH₂).

IR (ATR, cm⁻¹): 3051, 3011, 2920, 2854, 1668, 1327, 1165, 1108, 1065, 853, 753, 505cm⁻¹.

HRMS (ESI-TOF) m/z : Anal. Calcd for C₁₇H₁₃F₃N₃O: [M+H]⁺ 332.1011, found 332.1011.



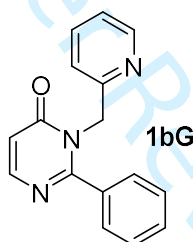
methyl 4-(6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-2-yl)benzoate 1bF: This compound was prepared according to the general procedure B with methyl 4-iodobenzoate (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 75% yield as a brown oil.

¹H NMR (CDCl₃, 300 MHz): δ = 8.46 (d, J = 4.2 Hz, 1H_{pyr}), 8.01-7.97 (m, 3H), 7.60-7.53 (m, 3H), 7.14 (dd, J = 6.9, 5.1 Hz, 1H_{pyr}), 7.08 (d, J = 7.8 Hz, 1H_{pyr}), 6.49 (d, J = 6.6 Hz, 1H, C5-H), 5.16 (s, 2H, N-CH₂), 3.87 (s, 3H, OCH₃).

¹³C NMR (CDCl₃, 75 MHz): δ = 166.1 (Cq), 161.7 (Cq), 160.9 (Cq), 154.7 (Cq), 152.4 (CH), 149.4 (CH), 138.7 (Cq), 136.6 (CH), 131.6 (Cq), 129.7 (2×CH_{arom}), 128.1 (2×CH_{arom}), 122.5 (CH), 121.6 (CH), 114.5 (CH), 52.4 (OCH₃), 50.6 (N-CH₂).

IR (ATR, cm⁻¹): 3057, 2947, 1721, 1672, 1425, 1276, 1104, 858, 758, 709 cm⁻¹.

HRMS (ESI-TOF) m/z : Anal. Calcd for C₁₈H₁₆N₃O₃: [M+H]⁺ 322.1197, found 322.1192.



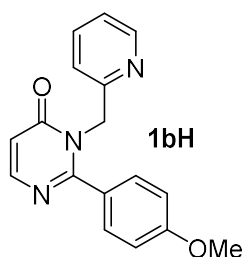
2-phenyl-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one 1bG: This compound was prepared according to the general procedure B with 4-iodobenzene (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 26% yield as a brown oil.

¹H NMR (CDCl₃, 300 MHz): δ = 8.49 (br s, 1H_{pyr}), 8.01 (d, J = 6.2 Hz, 1H, C6-H), 7.60 (t, J = 7.7 Hz, 1H_{pyr}), 7.46-7.39 (m, 3H), 7.36-7.31 (m, 2H), 7.15-7.07 (m, 2H), 6.50 (d, J = 6.5 Hz, 1H, C5-H), 5.23 (s, 2H, N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 162.1 (C=O), 155.3 (Cq), 152.6 (C6-H), 149.4 (CH_{pyr}), 136.6 (CH_{pyr}), 134.8 (Cq), 130.2 (CH_{arom}), 128.6 (2×CH_{arom}), 127.9 (2×CH_{arom}), 122.4 (CH_{pyr}), 121.5 (CH_{pyr}), 114.1 (C5-H), 50.9 (N-CH₂).

IR (ATR, cm⁻¹): 2959, 1672, 1524, 1485, 1431, 1044, 840, 766, 700, 497, 583 cm⁻¹.

HRMS (ESI-TOF) m/z : Anal. Calcd for C₁₆H₁₄N₃O [M+H]⁺ 264.1137, found 264.1136.



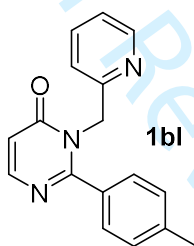
2-(4-methoxyphenyl)-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one 1bH: This compound was prepared according to the general procedure B with 4-iodoanisole (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 26% yield as a brown oil.

¹H NMR (CDCl₃, 300 MHz): δ = 8.51 (d, J = 4.2 Hz, 1H, CH_{pyr}), 8.00 (d, J = 6.5 Hz, 1H, C6-H), 7.63 (td, J = 7.7, 1.7 Hz, 1H, CH_{pyr}), 7.44 (d, J = 8.9 Hz, 2H, 2×CH_{arom}), 7.17 (dd, J = 7.1, 5.3 Hz, 1H, CH_{pyr}), 7.12 (d, J = 7.8 Hz, 1H, CH_{pyr}), 6.86 (d, J = 8.9 Hz, 2H, 2×CH_{arom}), 6.47 (d, J = 6.5 Hz, 1H, C5-H), 5.27 (s, 2H, N-CH₂), 3.80 (s, 3H, OCH₃).

¹³C NMR (CDCl₃, 75 MHz): δ = 162.4 (Cq), 162.0 (Cq), 161.2 (Cq), 155.5 (Cq_{pyr}), 152.6 (C6-H), 149.5 (CH_{pyr}), 136.8 (CH_{pyr}), 129.8 (2×CH_{arom}), 127.0 (Cq), 122.4 (CH_{pyr}), 121.6 (CH_{pyr}), 114.0 (2×CH_{arom}), 113.7 (C5-H), 55.5 (OCH₃), 51.2 (N-CH₂).

IR: 3051, 3005, 2920, 1668, 1500, 1254, 1180, 839 cm⁻¹.

HRMS: Anal. Calcd for C₁₇H₁₆N₃O₂: [M+H]⁺ 294.1243, found 294.1243.

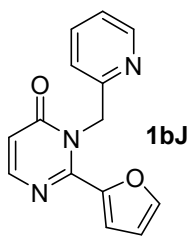


3-(pyridin-2-ylmethyl)-2-(p-tolyl)pyrimidin-4(3H)-one 1bI: This compound was prepared according to the general procedure B with 4-iodotoluene (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 34% yield as a brown oil.

¹H NMR (DMSO, 300 MHz): δ = 8.45 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 6.5 Hz, 1H), 7.71 (td, J = 7.7, 1.7 Hz, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.25 (dd, J = 7.0, 5.2 Hz, 1H), 7.20-7.16 (m, 3H), 6.45 (d, J = 6.5 Hz, 1H), 5.13 (s, 2H, N-CH₂), 2.30 (s, 3H, CH₃).

¹³C NMR (DMSO, 75 MHz): δ = 161.1 (C=O), 155.2 (Cq), 152.7 (CH), 148.9 (CH), 139.7 (Cq), 136.7 (CH), 132.1 (CH), 128.8 (2×CH), 127.7 (2×CH), 122.4 (CH), 121.4 (CH), 50.0 (N-CH₂), 20.8 (CH₃).

HRMS (ESI-TOF) m/z : calculated for C₁₇H₁₆N₃O [M+H] 278.1293 found 278.1287.

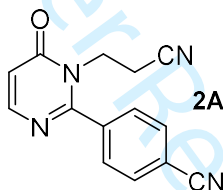


3-(pyridin-2-ylmethyl)-2-(thiophen-2-yl)pyrimidin-4(3H)-one 1bJ: This compound was prepared according to the general procedure B with 2-bromofuran (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 50% yield as a brown oil.

¹H NMR (CDCl₃, 300 MHz): δ = 8.54 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H_{pyr}), 8.02 (d, J = 6.5 Hz, 1H, C6-H), 7.65 (td, J = 7.7, 1.8 Hz, 1H), 7.50 (dd, J = 1.8, 0.8 Hz, 1H), 7.21-7.12 (m, 2H), 7.10 (dd, J = 3.6, 0.8 Hz, 1H), 6.47-6.45 (m, 2H, C5-H and CH_{arom}), 5.66 (s, 2H, N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): 162.2 (C=O), 155.6 (Cq), 152.9 (C6-H), 151.4 (Cq), 149.3 (CH_{pyr}), 146.6 (Cq), 145.5 (CH), 137.2 (CH), 122.5 (CH), 120.9 (CH), 117.3 (CH), 113.3 (CH), 112.2 (CH), 49.8 (N-CH₂).

HRMS (ESI-TOF) m/z : Anal. Calcd for C₁₄H₁₂N₃O₂ [M+H]⁺ 254.0930, found 254.0932.



4-(1-(2-cyanoethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)benzotrile 2A: This compound was prepared according to the general procedure C with 4-iodobenzotrile (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 52% yield as a white solid.

Aspect: white solid

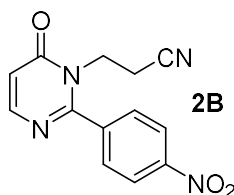
Mp: 165-166.7 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.01 (d, J = 6.6 Hz, 1H, C6-H), 7.86 (d, J = 8.6 Hz, 2H, 2×CH_{arom}), 7.68 (d, J = 8.6 Hz, 2H, 2×CH_{arom}), 6.55 (d, J = 6.6 Hz, 1H, C5-H), 4.19 (t, J = 6.4 Hz, 2H), 2.87 (t, J = 6.4 Hz, 2H).

¹³C NMR (CDCl₃, 75 MHz): δ = 161.3 (C=O), 159.2 (Cq, C2), 152.6 (C6-H), 137.7 (Cq), 132.9 (2×CH_{arom}), 129.4 (2×CH_{arom}), 117.6 (Cq), 116.5 (Cq, CN), 115.0 (C5-H), 114.9 (Cq), 42.1 (N-CH₂), 16.3 (CH₂).

IR (ATR, cm⁻¹): 2233, 1674, 1524, 1500, 1445, 1185, 852, 837, 589, 558, 541 cm⁻¹.

HRMS (ESI-TOF) m/z : calculated for C₁₄H₁₁N₄O [M+H]⁺ 251.0933 found 251.0927.



3-(2-(4-nitrophenyl)-6-oxopyrimidin-1(6H)-yl)propanenitrile 2B: This compound was prepared according to the general procedure C with 1-iodo-4-nitrobenzene (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 49% yield as a white solid.

Aspect: white solid

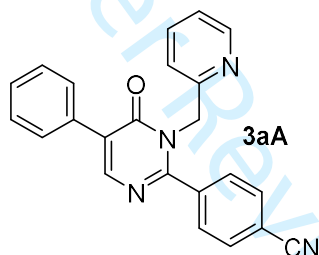
Mp: 191-193 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.40 (d, *J* = 8.6 Hz, 2H, 2×CH_{arom}), 8.01 (d, *J* = 6.5 Hz, 1H, C6-H), 7.75 (d, *J* = 8.6 Hz, 2H, 2×CH_{arom}), 6.55 (d, *J* = 6.6 Hz, 1H, C5-H), 4.20 (t, *J* = 6.3 Hz, 2H), 2.87 (t, *J* = 6.3 Hz, 2H).

¹³C NMR (CDCl₃, 75 MHz): δ = 161.3 (Cq), 158.9 (Cq), 152.6 (CH), 149.0 (Cq), 139.4 (Cq), 129.9 (2×CH_{arom}), 124.4 (2×CH_{arom}), 116.5 (Cq), 115.1 (CH), 42.1 (CH₂), 16.3 (CH₂).

IR (ATR, cm⁻¹): 3104, 1678, 1517, 1347, 1181, 863, 838, 752, 708, 458 cm⁻¹.

HRMS (ESI-TOF) *m/z*: calculated for C₁₃H₁₁N₄O₃ [M+H]⁺ 271.0831 found 271.0822.



4-(6-oxo-5-phenyl-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-2-yl)benzonitrile

3aA: This compound was prepared according to the general procedure B with 4-iodobenzonitrile (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 79% yield as a white solid.

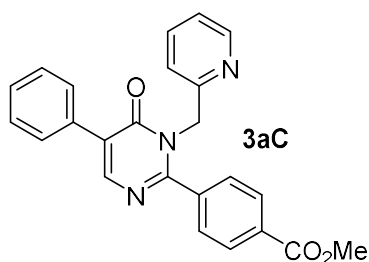
Aspect: white solid

Mp: 96-97 °C (CH₂Cl₂/EP)

¹H NMR (CDCl₃, 300 MHz): δ = 8.51 (d, *J* = 4.9 Hz, 1H_{pyr}), 8.20 (s, C6-H), 7.83 (d, *J* = 7.9 Hz, 2H_{arom}), 7.71-7.61 (m, 4H_{arom} and 1 CH_{pyr}), 7.44-7.32 (m, 3H_{arom}), 7.26-7.16 (m, 2H_{pyr}), 5.27 (s, N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 160.8 (Cq), 158.6 (Cq), 154.6 (Cq), 149.7 (CH), 149.5 (CH), 139.0 (Cq), 136.8 (CH_{pyr}), 132.9 (CH), 132.4 (2×CH_{arom}), 129.3 (CH_{arom}), 128.6 (CH_{arom}), 128.5 (2×CH_{arom}), 128.4 (2×CH_{arom}), 126.3 (Cq), 122.7 (CH_{pyr}), 122.4 (CH_{pyr}), 118.0 (Cq), 114.1 (Cq), 51.4 (N-CH₂).

IR (ATR, cm⁻¹): 2962, 2840, 2227, 1650, 1593, 1249, 1174, 1032, 836, 758, 569, 546, 415 cm⁻¹.



methyl 4-(6-oxo-5-phenyl-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-2-yl)benzoate **3aC**: This compound was prepared according to the general procedure B with methyl 4-iodobenzoate (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 59% yield as a white solid.

Aspect: white solid

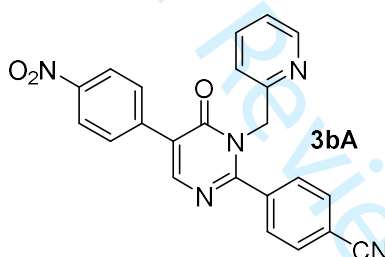
Mp: 137-139 °C (CH₂Cl₂/EP)

¹H NMR (CDCl₃, 300 MHz): δ = 8.50 (d, *J* = 4.8 Hz, 1H, CH_{pyr}), 8.21 (C6-H), 8.07 (d, *J* = 8.5 Hz, 2H, 2×CH_{arom}), 7.72-7.68 (m, 4H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H, CH_{pyr}), 7.43-7.34 (m, 3H), 7.19-7.13 (m, 2H), 5.24 (N-CH₂), 3.91 (OCH₃).

¹³C NMR (CDCl₃, 75 MHz): δ = 166.2 (C=O, CO₂Me), 161.0 (Cq), 159.6 (Cq), 154.9 (Cq), 149.8 (CH), 149.4 (CH), 138.9 (Cq), 136.7 (CH), 133.1 (Cq), 131.6 (Cq), 129.8 (2×CH_{arom}), 128.5 (2×CH_{arom}), 128.4 (CH), 128.4 (CH), 125.95 (Cq), 122.5 (CH_{pyr}), 121.9 (CH_{pyr}), 52.4 (OCH₃), 51.4 (N-CH₂).

IR (ATR, cm⁻¹): 2923, 2850, 2344, 1667, 1467, 1279, 1109, 787, 696, 633, 425 cm⁻¹.

HRMS (ESI-TOF) *m/z*: calcd for C₂₄H₂₀N₃O₃: [M+H]⁺ 398.1505; found 398.1505.



4-(5-(4-nitrophenyl)-6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-2-yl)benzonitrile **3bA**: This compound was prepared according to the general procedure B with 4-iodobenzonitrile (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 45% yield as a yellow solid.

Aspect: yellow solid

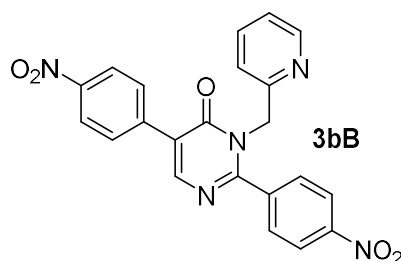
Mp: 196 – 198 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.53 (d, *J* = 4.4 Hz, 1H, CH_{pyr}), 8.29 (s, 1H, C6-H), 8.26 (d, *J* = 8.8 Hz, 2H, 2×CH_{arom}), 7.91 (d, *J* = 8.8 Hz, 2H, 2×CH_{arom}), 7.86 (d, *J* = 8.3 Hz, 2H, 2×CH_{arom}), 7.73 (d, *J* = 8.3 Hz, 2H, 2×CH_{arom}), 7.68 (td, *J* = 7.8, 1.4 Hz, 1H, CH_{pyr}), 7.27-7.20 (m, 2H, 2×CH_{pyr}), 5.23 (s, 2H, N-CH₂)

¹³C NMR (CDCl₃, 75 MHz): δ = 160.4 (Cq), 160.1 (Cq), 154.1 (Cq), 151.0 (CH, C6-H), 149.6 (CH_{pyr}), 147.6 (Cq), 139.7 (Cq), 138.7 (Cq), 137.1 (CH_{pyr}), 132.5 (2×CH_{arom}), 129.3 (2×CH_{arom}, 2×CH_{arom}), 124.1 (Cq), 123.7 (2×CH_{arom}), 123.0 (CH_{pyr}), 122.5 (CH_{pyr}), 117.9 (Cq), 114.5 (Cq), 51.5 (N-CH₂).

IR (ATR, cm⁻¹): 2985, 2229, 1670, 1504, 1340, 849, 751, 550 cm⁻¹.

HRMS (ESI-TOF) *m/z*: calcd for C₂₃H₁₆N₅O₃: [M+H]⁺ 410.1253; found 410.1240.



2,5-bis(4-nitrophenyl)-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one 3bB: This compound was prepared according to the general procedure B with 1-iodo-4-nitrobenzene (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 26% yield as a grey solid.

Aspect: grey solid

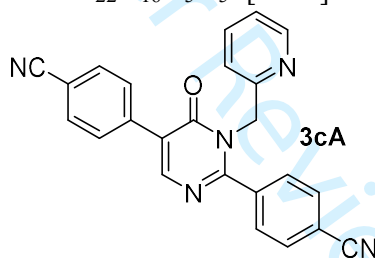
Mp: 201 – 203 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.53 (d, *J* = 4.2 Hz, 1H, CH_{pyr}), 8.30-8.24 (m, 5H, 2×CH_{arom}, 2×CH_{arom}, C6-H), 7.95-7.90 (m, 4H, 2×CH_{arom}, 2×CH_{arom}), 7.68 (td, *J* = 7.7, 1.8 Hz, 1H, CH_{pyr}), 7.28-7.21 (m, 2H, 2×CH_{pyr}), 5.24 (N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 160.4 (Cq), 159.9 (Cq), 154.1 (Cq), 150.9 (CH, C6-H), 149.6 (CH_{pyr}), 149.0 (Cq), 147.7 (Cq), 140.4 (Cq), 139.7 (139.7 (Cq), 137.1 (CH_{pyr}), 129.8 (2×CH_{arom}), 129.3 (2×CH_{arom}), 124.3 (Cq), 123.9 (2×CH_{arom}), 123.7 (2×CH_{arom}), 123.1 (CH_{pyr}), 122.5 (CH_{pyr}), 51.5 (N-CH₂).

IR (ATR, cm⁻¹): 3314, 3011, 1668, 1513, 1346, 850, 761, 713 cm⁻¹.

HRMS (ESI-TOF) *m/z*: calcd for C₂₂H₁₆N₅O₅: [M+H]⁺ 430.1151; found 430.1162.



4,4'-(6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidine-2,5-diyl)dibenzonitrile 3cA: This compound was prepared according to the general procedure B with 4-iodobenzonitrile (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 34% yield as a yellow solid.

Aspect: yellow solid

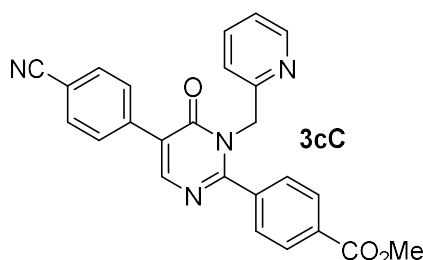
Mp: 204 – 206.5 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.52 (d, *J* = 4.8 Hz, 1H, CH_{pyr}), 8.25 (s, 1H, C6-H), 7.86-7.82 (m, 4H, 2×CH_{arom}, 2×CH_{arom}), 7.73-7.63 (m, 5H, 2×CH_{arom}, 2×CH_{arom}, CH_{pyr}), 7.26-7.18 (m, 2H, 2×CH_{pyr}), 5.22 (s, 2H, N-CH₂).

¹³C NMR (CDCl₃, 75 MHz): δ = 160.4 (Cq), 159.9 (Cq), 154.2 (Cq), 150.7 (C6-H), 149.6 (CH_{pyr}), 138.7 (Cq), 137.8 (Cq), 137.0 (CH_{pyr}), 132.5 (2×CH_{arom}), 132.2 (2×CH_{arom}), 129.3 (2×CH_{arom}), 129.1 (2×CH_{arom}), 124.4 (Cq), 122.9 (CH_{pyr}), 122.5 (CH_{pyr}), 118.8 (Cq), 117.9 (Cq), 114.5 (Cq), 112.0 (Cq), 51.5 (N-CH₂).

IR (ATR, cm⁻¹): 2227, 1670, 1503, 839, 560, 417 cm⁻¹.

HRMS (ESI-TOF) *m/z*: calcd for C₂₄H₁₆N₅O: [M+H]⁺ 390.1355; found 390.1363.



methyl 4-(5-(4-cyanophenyl)-6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-2-yl)benzoate 3cC: This compound was prepared according to the general procedure B with methyl 4-iodobenzoate (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 27% yield as a yellow solid.

Aspect: yellow solid

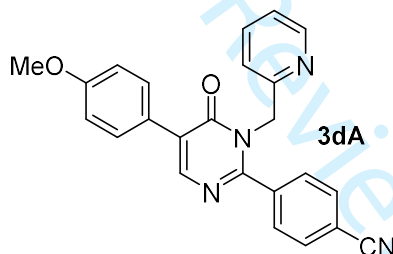
Mp: 213 – 216 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.51 (d, *J* = 3.6 Hz, 1H, CH_{pyr}), 8.26 (s, 1H, C6-H), 8.08 (d, *J* = 8.3 Hz, 2H, 2×CH_{arom}), 7.85 (d, *J* = 8.5 Hz, 2H, 2×CH_{arom}), 7.72 (d, *J* = 8.4 Hz, 2H, 2×CH_{arom}), 7.69 (d, *J* = 8.3 Hz, 2H, 2×CH_{arom}), 7.66-7.60 (m, 1H, CH_{pyr}), 7.20-7.17 (m, 2H, CH_{pyr}), 5.25 (s, 2H, N-CH₂), 3.92 (s, 3H, OCH₃).

¹³C NMR (CDCl₃, 75 MHz): δ = 166.2 (Cq, CO₂Me), 161.0 (Cq), 160.6 (Cq), 154.5 (Cq), 150.9 (C6-H), 149.6 (CH_{pyr}), 138.6 (Cq), 138.0 (Cq), 136.9 (CH_{pyr}), 132.2 (2×CH_{arom}), 131.9 (Cq), 129.9 (2×CH_{arom}), 129.1 (2×CH_{arom}), 128.4 (2×CH_{arom}), 124.1 (Cq), 122.7 (CH_{pyr}), 122.0 (CH_{pyr}), 118.8 (Cq), 111.9 (Cq), 52.5 (OCH₃), 51.5 (N-CH₂).

IR (ATR, cm⁻¹): 2999, 2952, 2227, 1720, 1665, 1272, 1098, 847, 778, 754, 559, 526 cm⁻¹.

HRMS (ESI-TOF) *m/z*: calcd for C₂₅H₁₉N₄O₃: [M+H]⁺ 423.1457; found 423.1444.



4-(5-(4-methoxyphenyl)-6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-2-yl)benzonitrile 3dA: This compound was prepared according to the general procedure B with 4-iodobenzonitrile (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 51% yield as a yellow solid.

Aspect: yellow solid

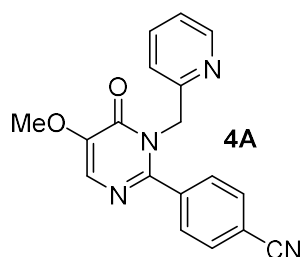
Mp: 188 – 190 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.51 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1H, CH_{pyr}), 8.16 (s, C6-H), 7.82 (d, *J* = 8.6 Hz, 2H, 2×CH_{arom}), 7.71-7.64 (m, 4H_{arom} and 1CH_{pyr}), 7.26-7.16 (m, 2H, 2×CH_{pyr}), 6.94 (d, *J* = 8.9 Hz, 2H, 2×CH_{arom}), 5.21 (s, 2H, N-CH₂), 3.82 (s, 3H, OCH₃).

¹³C NMR (CDCl₃, 75 MHz): δ = 161.0 (Cq), 160.0 (Cq), 158.0 (Cq), 154.8 (Cq), 149.5 (CH_{pyr}), 148.8 (C6-H), 139.2 (Cq), 136.9 (CH_{pyr}), 132.4 (2×CH_{arom}), 129.9 (2×CH_{arom}), 129.4 (2×CH_{arom}), 126.0 (Cq), 125.3 (Cq), 122.8 (CH_{pyr}), 122.4 (CH_{pyr}), 118.1 (Cq), 114.1 (Cq), 114.0 (2×CH_{arom}), 55.4 (OCH₃), 51.4 (N-CH₂).

IR (ATR, cm⁻¹): 2905, 2227, 1670, 1503, 1429, 838, 758, 558, 415 cm⁻¹.

HRMS (ESI-TOF) *m/z*: calcd for C₂₄H₁₉N₄O₂: [M+H]⁺ 395.1508; found 395.1506.



5-methoxy-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one 4A: This compound was prepared according to the general procedure B with 4-iodobenzonitrile (1.2 eq) as halide. The crude product was purified by flash chromatography to afford the title compound in 67% yield as an orange solid.

Aspect: orange solid

Mp = 171 – 174 °C (CH₂Cl₂/Pentane)

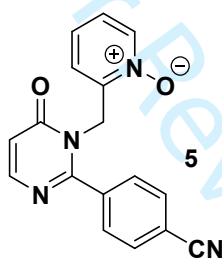
¹H NMR (CDCl₃, 300 MHz): δ = 8.46 (dd, *J* = 5.2, 1.6 Hz, 1H_{pyr}), 7.64-7.58 (m, 4H_{arom} and 1H_{pyr}), 7.53 (C6-H), 7.18-7.14 (m, 2H_{pyr}), 5.17 (s, 2H, N-CH₂), 3.89 (s, 3H, OCH₃).

¹³C NMR (CDCl₃, 75 MHz): 157.9 (C=O), 154.5 (C_q_{pyr}), 151.2 (C_q, C2), 149.5 (CH_{pyr}), 146.2 (C_q, C5), 139.0 (C_q), 136.8 (CH_{pyr}), 132.3 (2×CH_{arom}), 129.4 (2×CH_{arom}), 127.7 (CH), 122.8 (CH_{pyr}), 122.3 (CH_{pyr}), 118.1 (C_q), 113.8 (C_q), 56.5 (OCH₃), 50.9 (N-CH₂).

IR (ATR, cm⁻¹): 3037, 2946, 2222, 2112, 1674, 1594, 1425, 1250, 1077, 840, 757, 560 cm⁻¹.

HRMS: Anal. Calcd for C₁₈H₁₄N₄O₂: [M+H]⁺ 319.1195 found 319.1193.

5. Deprotection of the pyridinyl group



2-((2-(4-cyanophenyl)-6-oxopyrimidin-1(6H)-yl)methyl)pyridine 1-oxide 5: To a solution of 4-(6-oxo-1-(pyridin-2-ylmethyl)-1,6-dihydropyrimidin-2-yl)benzonitrile (0.2 g, 0.71 mmol) in DCM (20 mL), *m*-CPBA 70% (0.2 g, 1.2 mmol) is added at 0°C. The mixture is stirred at room temperature overnight. K₂CO₃ (0.116 g, 0.85 mmol) is added and stirred during 10 min. The solution is filtered and evaporated in vacuo to obtain a pale-yellow solid (0.2025 g, 95%).

Aspect: pale yellow solid.

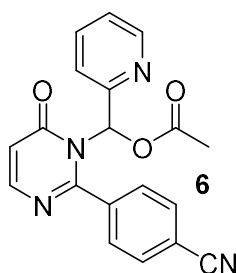
Mp: 196 – 199 °C (CH₂Cl₂/Pentane)

¹H NMR (CDCl₃, 300 MHz): δ = 8.12 (d, *J* = 5.8 Hz, 1H), 7.98 (d, *J* = 6.5 Hz, 1H, C6-H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.41-7.38 (m, 1H), 7.31-7.22 (m, 2H), 6.46 (d, *J* = 6.5 Hz, 1H, C5-H), 5.24 (s, 2H, N-CH₂).

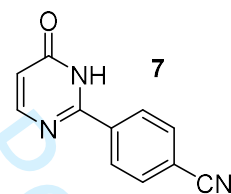
¹³C NMR (CDCl₃, 75 MHz): δ = 161.7, 160.3, 152.4, 144.4, 139.4, 138.8, 132.4 (2×CH_{arom}), 128.8 (2×CH_{arom}), 127.0, 125.6, 125.3, 117.8, 114.6, 114.2, 46.7 (N-CH₂).

IR (ATR, cm⁻¹): 2771, 2228, 1652, 1499, 1244, 982, 837, 765, 497, 443 cm⁻¹.

HRMS (ESI-TOF) *m/z*: Anal. Calcd for C₁₇H₁₃N₄O₂: [M+H]⁺ 305.1039, found 305.1033.



(2-(4-cyanophenyl)-6-oxopyrimidin-1(6H)-yl)(pyridin-2-yl)methyl acetate 6: 2-((2-(4-cyanophenyl)-6-oxopyrimidin-1(6H)-yl)methyl)pyridine 1-oxide (0.2025 g, 0.6 mmol) was treated with Ac₂O (20 mL) at 140°C during 18 h. The crude product was filtered through a short pad of silica gel and used immediately for the next step.



4-(6-oxo-1,6-dihydropyrimidin-2-yl)benzonitrile 7: to a solution of (2-(4-cyanophenyl)-6-oxopyrimidin-1(6H)-yl)(pyridin-2-yl)methyl acetate (0.184 g, 0.53 mmol) in THF/H₂O (4:1) was added LiOH (0.0127 g, 0.53 mmol) and it was stirred at 35 °C during 10 minutes. Then, it was heated at 110 °C during 45 minutes. After the mixture was cooled, AcOH (0.03 mL, 0.53 mmol) was added. After evaporation in vacuo, the product was purified by flash column chromatography through silica gel using AcOEt/DCM (6:4) to give the title compound as a white solid (0.092 g, 88%).

Aspect: White powder

Mp: 234-237 °C (CH₂Cl₂/EP)

¹H NMR (CDCl₃, 300 MHz): δ = 8.36 (d, *J* = 8.7 Hz, 2H, 2×CH_{arom}), 8.19 (d, *J* = 6.6 Hz, 1H, C6-H), 7.86 (d, *J* = 8.7 Hz, 2H, 2×CH_{arom}), 6.53 (d, *J* = 6.6 Hz, 1H, C5-H).

¹³C NMR (CDCl₃, 75 MHz): δ = 165.04 (Cq), 155.9 (Cq), 155.8 (C6-H), 135.8 (Cq), 132.9 (2×CH_{arom}), 128.5 (2×CH_{arom}), 118.1 (Cq), 115.7 (Cq), 114.8 (C5-H).

IR (ATR, cm⁻¹): 3047, 2927, 2849, 2227, 1667, 1591, 1548, 985, 840, 532 cm⁻¹.

HRMS (ESI-TOF) *m/z*: Anal. Calcd for C₁₁H₈N₃O: [M+H]⁺ 198.0666, found 198.0667.

6. Deprotection of the ethylcyano group

To a suspension of cyanoethylated compound **2A** (250 mg, 1 mmol) in 5 mL diethylamine, was added DBU (15 mg, 0.1 mmol). After heating 16 hrs at 60°C (sealed tube), evaporation of diethylamine followed by flash chromatography through silica gel gave **7** (40 mg, 20 % yield).

7. Copies of NMR Spectra

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