Full Paper

An efficient phosphorus-free chlorination of hydroxy aza-arenes and its application in one-pot pharmaceutical synthesis

Jian Wang, Yan-Hui Li, Song-Cheng Pan, Ming-Fang Li, Wenting Du, Hong Yin, and Jing-Hua Li

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.9b00407 • Publication Date (Web): 17 Jan 2020

An efficient phosphorus-free chlorination of hydroxy aza-arenes and its application in one-pot pharmaceutical synthesis

Jian Wang[†, ‡, #], Yan-Hui Li[†, #], Song-Cheng Pan[†], Ming-Fang Li[†], Wenting Du[‡], Hong Yin[‡], Jing-Hua Li[†, *]

[†] College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, PR China

[‡] School of Pharmacy, Hangzhou Medical College, Hangzhou 310053, PR China

# These authors contributed equally to this work

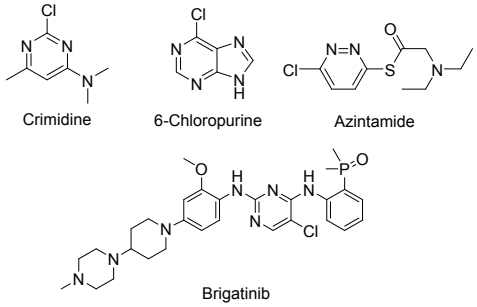
* Corresponding author. Email: lijh@zjut.edu.cn

ABSTRACT: The chlorination of hydroxy aza-arenes with BTC and $SOCl_2$ has been effectively performed by refluxing with 5 wt% DMAP as catalyst. Various substrates are chlorinated with high yields. The obtained chlorinated aza-arenes can be used directly with simple workup for succedent one-pot synthesis in large scale.

KEYWORDS: phosphorus-free chlorination; hydroxy aza-arenes; simple workup; one-pot synthesis

INTRODUCTION

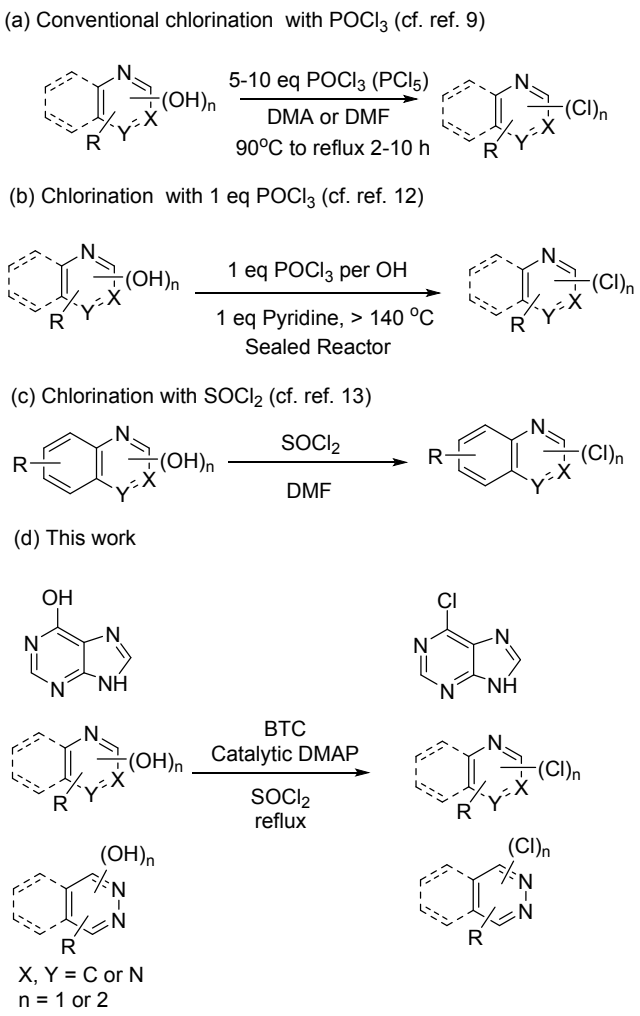
Chlorinated aza-arenes can be used as active ingredients in many agrochemicals,[1] pharmaceuticals,[2] and other functional chemicals[3]. As reactive intermediates, they also have been widely applied for building carbon-carbon bond and carbon-hetero bond by direct reactions with nucleophile,[4] or through organometallic reactions such as Suzuki coupling,[5] Stille reaction,[6] Heck reaction,[7] etc.[8] (Scheme 1)



Scheme 1. Examples of chlorinated aza-arenes as functional molecules or their key intermediates.

The conventional method for synthesizing chlorinated heterocycles includes direct substitution of the hydroxy group of their corresponding compounds with $POCl_3$ or PCl_5.[9] Reaction conditions for these chlorinations have little changed over past 100 years, [10] which usually involve tertiary amine (or amide) as catalyst and large excess $POCl_3$ as solvent (Scheme 2-a). The waste which contains phosphorus thus produced in industry usually causes eutrophication of aquatic ecosystems and stricter limitations of phosphorus-contained industrial wastewater discharge has been set worldwide. [11a, 11b, 11c, 11d, 11e] Although the amount of $POCl_3$ can be reduced to 1 eq when reaction takes place in high temperature in a sealed reactor with stoichiometric base (Scheme 2-b),[11f, 11g] the inconvenient workup of handling $POCl_3$ /catalyst after reaction and the phosphorus-containing waste limits its industrial application due to the evergrowing environmental requirements.

One alternative for replacing $POCl_3$ as the chlorinating agent/solvent is $SOCl_2$, waste of which are HCl and SO_2 without any phosphorus.[12] Moreover, SO_2 can be removed through our previously reported process.[12a] However, the scope of reported $SOCl_2$-chlorination substrates is confined to quinoxalines,[12b, 12c] quinazolines,[12d] etc.[12e] (Scheme 2-c). All of these substrates are benzoazaheterocycles, the only exception disclosed is chlorination of pyridines with narrow substrate scope.[12f] As a cheap and stable chlorinating agent for various substrates, BTC (bis(trichloromethyl) carbonate, solid phosgene) has been widely used in chemical industry as a replacement for phosgene.[13] Nevertheless, it has seldom been used for chlorination of hydroxy aza-arenes. Herein, we report an efficient chlorination system for hydroxy aza-arenes with BTC/$SOCl_2$ (Scheme 2-d).

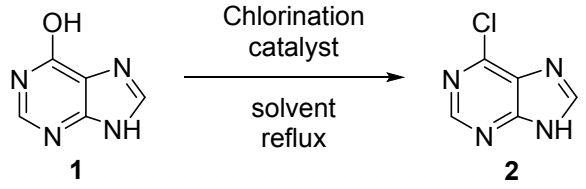


Scheme 2. Some representative chlorinations of hydroxy aza-arenes.

RESULTS AND DISCUSSION

1. Optimization of reaction conditions. At the beginning of our investigation, hypoxanthine (**1**) was chosen as the model substrate to synthesize 6-chloropurine (**2**), a key intermediate for many medicines and bioactive compounds, since it is hard to carry out this conversion by many conventional agent(s) due to its extremely poor solubility of **1** in many solvents.[14] According to the literature,[15] $POCl_3$/DMA (N,N-dimethylaniline) was optimized for chlorination of hypoxanthine **1**, which was confirmed by our experiment as shown in Table 1 (Table 1, entry 1). Replacing $POCl_3$ with $SOCl_2$ as solvent ($POCl_3$/$SOCl_2$) causes significant decrease of product yield (Table 1, entries 2-3). However, BTC/$SOCl_2$ (a solution of BTC in $SOCl_2$) is effective for this reaction, especially, in the presence of 4-dimethylaminopyridine (DMAP), which shows best catalytic activity (Table 1, entry 4, and Table S1 of Supporting Information). Other solvent rather than $SOCl_2$ in this system while shows much less efficiency (See details in Table S1 of Supporting Information). It reveals that the reaction proceeds poorly if any component of the chlorination system of BTC/$SOCl_2$/DMAP missed (Table 1, entries 5-7). Particularly, BTC/$SOCl_2$/DMAP is more effective than $POCl_3$ system for this conversion (Table 1, entries 4 and 1), the resulting mixture of the latter is a black and viscous solution with vast amount of phosphorus-containing wastewater after workup (Table 1, entry 1). Whereas BTC/$SOCl_2$ reaction only results in a slight yellow clear solution, which gives light yellow powder after evaporation of the solvent (Table 1, entry 4). Besides, as a solvent, most $SOCl_2$ can be recovered by evaporation in this BTC/$SOCl_2$/DMAP system after reaction, this is particularly conductive to its industrial application. Thus we choose 6-hydroxypurine (1 g), 1 equimolar BTC (1 equimolar for each hydroxy group), 5 wt. % DMAP and 8 mL $SOCl_2$ under reflux as optimized condition for the following substrate scope investigation.

Table 1. **Optimization of hypoxanthine chlorination.**[a]



entry	chlorination reagent	solvent	catalyst	yield %[b]
1 [c,d]	$POCl_3$	$POCl_3$	DMA	94
2 [c,d]	$POCl_3$	$SOCl_2$	DMA	31
3 [c,d]	$POCl_3$	$SOCl_2$	DMAP	42
4[e]	BTC	$SOCl_2$	DMAP	96 (90)
5	$SOCl_2$	$SOCl_2$	DMAP	15
6	BTC	$SOCl_2$	DMA	29
7	BTC	toluene	DMAP	25

[a] Reaction conditions: substrate (1 g), chlorination reagent (1 equimolar), catalyst (5 wt. %), solvent (8 mL).

[b] Determined by HPLC. Number in the parenthesis is isolated yield.

[c] Reaction conditions: substrates (1 g), chlorination reagent (3 equimolar), catalyst (5 wt. %), solvent (5 mL).

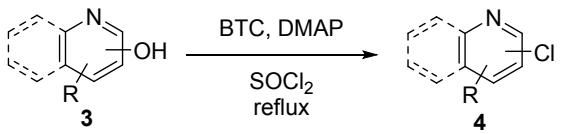
[d] Reaction presents heterogenous and turbid mixture during entire process.

[e] Reaction mixture becomes clear solution after several hours.

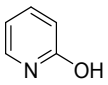
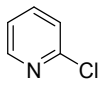
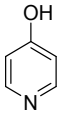
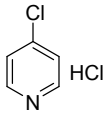
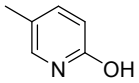
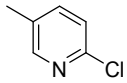
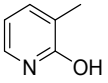
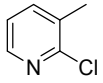
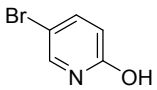
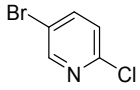
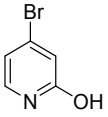
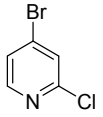
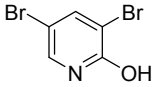
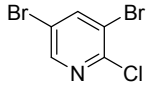
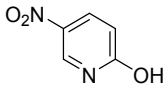
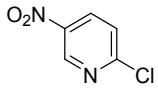
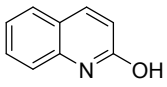
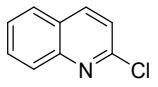
2. Substrate scope extension. Our attempt to explore the scope of the substrates started with pyridines, monoaza-arenes. As shown in Table 2, the hydroxy group on pyridines can be converted to chloro- by BTC/$SOCl_2$/DMAP in good yields (Table 2, entries 1-2). The substrates with electron-donating group (EDG, Table 2, entries 3-4) and electron-withdrawing group (EWG, Table 2, entries 5-8) all result in decent yields, while the substrates with EDG convert to corresponding chlorinated product much faster (Table 2, entries 1-4). Correspondingly, electron-deficient pyridine derivatives proceed with longer reaction time (not strictly) and slightly lower yields (Table 2, entries 5-8). This protocol also applies to

hydroxy benzopyridine (quinoline) with excellent result (Table 2, entry 9).

Table 2. **Chlorination of hydroxy pyridines with BTC/$SOCl_2$.**[a]



3 **4**

entry	substrate	time (h)	product	yield (%)[b]
1	 **3a**	4	 **4a**	89
2	 **3b**	3.5	 **4b**	94[c]
3	 **3c**	1	 **4c**	95
4	 **3d**	1.5	 **4d**	93
5	 **3e**	5	 **4e**	93
6	 **3f**	4.5	 **4f**	95
7	 **3g**	5	 **4g**	91
8	 **3h**	7	 **4h**	87
9	 **3i**	3	 **4i**	91

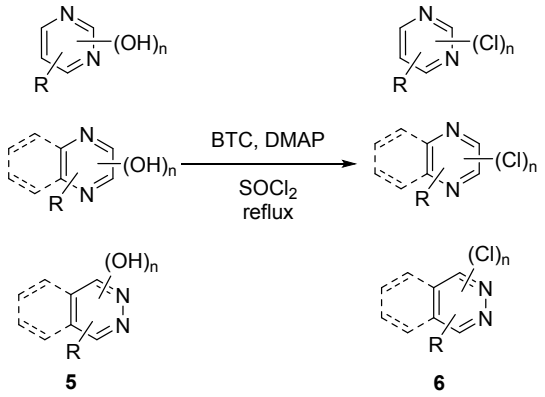
[a] Reaction conditions: **3** (1 g), BTC (1 equimolar), DMAP (5 wt. %), $SOCl_2$ (8 mL), reflux (90 °C oil bath).

[b] Isolated yield.

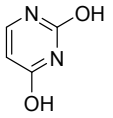
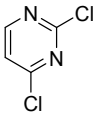
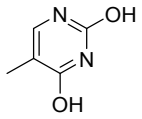
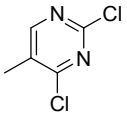
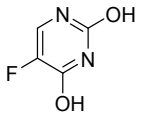
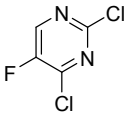
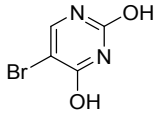
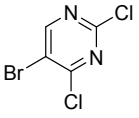
[c] Product obtained in hydrochloride salt form.

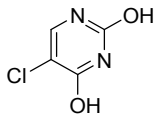
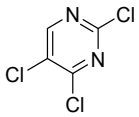
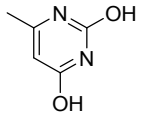
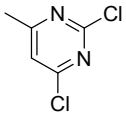
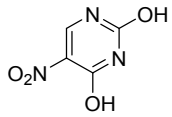
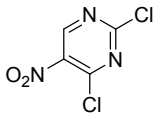
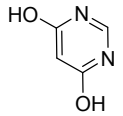
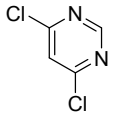
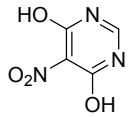
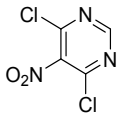
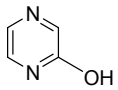
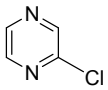
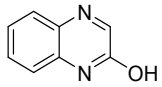
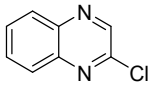
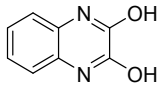
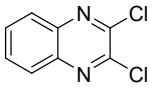
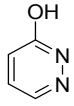
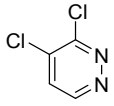
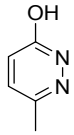
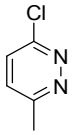
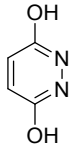
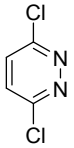
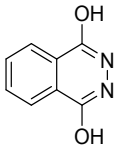
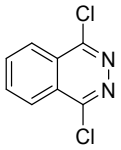
Next, the scope of the substrates was extended with diaza-arenes, such as pyrimidine, pyridazine and pyrazine derivatives. All substrates tested can be converted to chlorinated ones with good yields (Table 3). For substrates with same heterocyclic nucleus, the benzo-substrates react faster than monocyclic ones (Table 3, compare entry 10 with 11, entry 15 with 16). Dichlorination proceeds slower than monochlorination for same heterocyclic ring (Table 3, entries 11-12). Same as pyridine derivatives, substrates with EWG group proceeds more moderately, especially nitro-substituted ones (Table 3, entries 3-5, 7, 9). Notably, mono- hydroxy pyridazine **5m** gives ortho-dichloropyridazine **6m** as major product, which means the hydrogen next to hydroxy group on the ring is also substituted by chlorine (Table 3, entry 13). While structurally similar pyridazine **5n** only results in monochloropyridazine **6n** (Table 3, entry 14). And **5m** only converts to 3-chloropyridazine when $POCl_3$ is used as chlorinating agent.[16a] The possible mechanism might be involved in a disproportional reaction of $SOCl_2$, which needs to be further studied.

Table 3. **Substrate expansion of BTC/$SOCl_2$ chlorination.**[a]



5 **6**

entry	substrate	time (h)	product (**6**)	yield (%)[b]
1	 **5a**	9.5	 **6a**	95
2	 **5b**	8	 **6b**	93
3	 **5c**	10	 **6c**	87
4		12.5		90

	5d		**6d**	
5		10		91
	5e		**6e**	
6		7.5		92
	5f		**6f**	
7		13.5		75
	5g		**6g**	
8		7.5		95
	5h		**6h**	
9		14		72
	5i		**6i**	
10[c]		10.5		89
	5j		**6j**	
11[c]		6.5		94
	5k		**6k**	
12		8		93
	5l		**6l**	
13[c]		10		85
	5m		**6m**	
14[c]		9.5		93
	5n		**6n**	
15		11		94
	5o		**6o**	
16		8		97
	5p		**6p**	

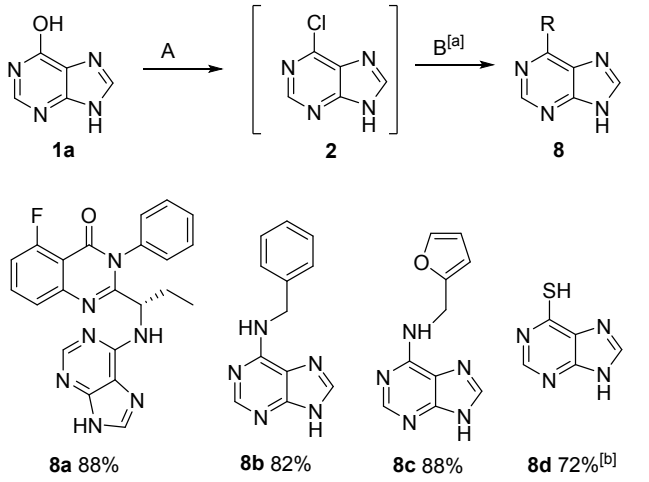
[a] Conditions: **5** (1g), BTC (2 equimolar), DMAP (5 wt %), $SOCl_2$ (8 mL), reflux (90 °C oil bath), 12h.

[b] Isolated yield.

[c] 1 equimolar BTC is used.

3. Application in one-pot pharmaceutical synthesis. The comparatively broad substrate scope and simple workup of this method prompt us to synthesize some functional molecules in a large scale. 6-Substituted purines are important bioactive molecules, e.g., idelalisib (**8a**) is the first PI3K-δ inhibitor and approved by FDA in 2014 for treatment of blood cancer.[16b, 16c, 16d, 16e] Traditional methods to obtain this compound require two-step synthesis where hypoxanthine (**1**) is chlorinated with $POCl_3$ and the resulting product 6-chloropurine is isolated as intermediate before next step after quenching with water.[16f, 16g] The drawback is obvious: cumbersome process including quenching with water, filtration, pH adjusting, etc. are needed for isolation of the intermediate **2**, and excessive phosphor-containing waste is produced simultaneously. While with BTC/$SOCl_2$/DMAP system, the protocol can be simplified as a one-pot two-step synthesis: $SOCl_2$ was removed after the complete conversion of 50 gram **1**, after which reactants **7** are added directly to the mixture without isolation; then exhaustion of the intermediate **2** is monitored by TLC, followed with simple workup and recrystallization to give the final product **8** in good yields without chromatographic isolation, which validate its possibility of industrial application (Scheme 3). Besides **8a**, several bioactive molecules also contains 6-substitued purine structure: 6-benzylaminopurine (**8b**) is the first synthetic cytokinin,[14a, 17] kinetin (**8c**) is a cytokinin plant growth regulator[14c, 18] and mercaptopurine (**8d**) is a highly effective antineoplastic agent for cancer and autoimmune diseases,[14b, 19] they can all be obtained from 6-substituted purines as a reaction substrate using the same method as idelalisib (**8a**). The products obtained by BTC/$SOCl_2$/DMAP system is identical to the products obtained by $POCl_3$/DMA system. Besides, other hydroxyaromatic heterocyclic compounds can be also reacted by the system to obtain corresponding derivatives.

The possible mechanism of this chlorination was summarized in Scheme 4 using hypoxanthine (**1**) as the model substrate based on reported literature.[20] Substrate is activated by BTC and then DMAP to form the pyridium intermediate **1c**, which finally release CO_2 and DMAP to form the chlorinated product **2.**

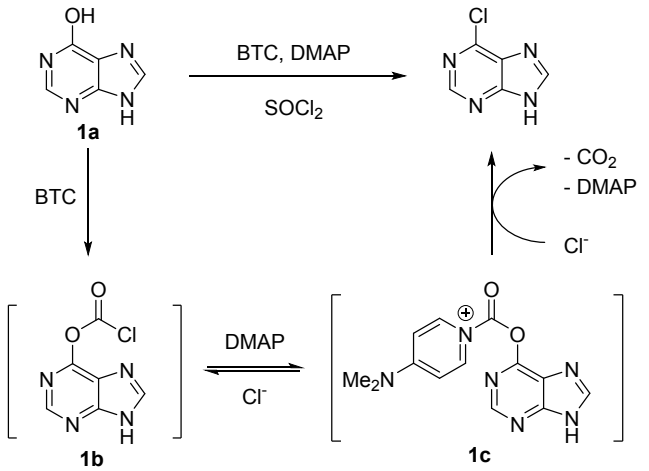


Conditions: A: **1a** (50 g), BTC (100 g), DMAP (2.5 g), $SOCl_2$ (400 mL), reflux (90 °C oil bath); B: Et_3N (74 g), ethanol (100 mL) ,**7** (1.2 equimolar), yield of isolated product.

[a] **7a** (for synthesizing **8a**): (S)-2-(1-aminopropyl)-5-fluoro-3-phenylquinazolin-4(3*H*)-one; **7b** (for synthesizing **8b**): benzylamine; **7c** (for synthesizing **8c**): furfurylamine; **7d** (for synthesizing **8d**): thiocarbamide;

[b] No Et_3N added in second step.

Scheme 3. Large-scale application of BTC/$SOCl_2$ chlorination in one-pot pharmaceutical synthesis.



Scheme 4. Possible mechanism of BTC/DMAP chlorination system.

CONCLUSION

In summary, we have developed a phosphorus-free system of BTC/$SOCl_2$/DMAP for chlorination of hydroxy aza-arenes. Its broad substrate scope as well as comparatively simple process and workup indicate its environmentally friendly applicability in chemical industry and pharmaceutical manufacturing. Four examples of large scale one-pot synthesis of bioactive molecules were also conducted. The chlorinated aza-arenes thus obtained, in many cases, can be used directly as substrate for succeeding synthesis without further purification, in which the residual DMAP might also be used as the catalyst. Our next plan will emphasize on studying the selectivity and mechanism of this chlorination system.

EXPERIMENTAL DETAILS

All reagents were purchased from commercial suppliers and used without further purification. Condensing of solvent during reaction was carried with cooling liquid circulator DLSB-5/20. Analytical TLC was performed with silica gel GF254 plates. HPLC was performed by TECHCOMP LC2000 (column: Diamonsil C8 (2) 250*4.6 mm) with methanol: water: acetonitrile = 5: 90: 5 as eluant. Melting point were recorded on melting point apparatus X-4. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Model Avance III 500M and 126 MHz or Ascend Bruker 600 MHz and 151 MHz spectrometers. Chemical shifts were recorded in $CDCl_3$, or DMSO-d_6 solutions referenced to tetramethylsilane (TMS) (0.00 ppm) or $CDCl_3$ (7.26 ppm), DMSO-d_6 (2.50 ppm), D_2O (4.79 ppm) for ^{1}H NMR, $CDCl_3$ (77 ppm) and DMSO-d_6 (39.5 ppm) for ^{13}C NMR. Flash chromatography was carried out with silica gel (200-300 mesh).

General procedure of chlorination. To a 50 mL round-bottomed flask with substrate 1000 mg, DMAP 50 mg, $SOCl_2$ 4 mL, and BTC/$SOCl_2$ solution (1 equimolar BTC per reactive OH dissolved in 4 mL $SOCl_2$) was added dropwise under reflux with low-temperature-condenser (with circulating coolant at -10~-20 °C, for large-scale preparation, with a normal condenser connected with a low-temperature-condenser on the top), and refluxing for certain hours after addition.

Post-reaction workup for chlorination.

*Post-reaction workup for products except **2** and **4b**.* After completion of the reaction monitored by TLC, the solvent was removed and the residue was quenched with cold water (0 °C, 10 mL) and adjusted to pH 8-9 with saturated Na_2CO_3 solution (Except for hydrochloride salt **4b**). The mixture was then extracted with dichloromethane (Except **2** and **4b**), dried with Na_2SO_4. Finally, solvent was removed by rotary evaporator and product was obtained by column chromatography on silica gel.

*Workup for **2**.* After completion of the reaction monitored by TLC, the solvent was removed and the residue was quenched with cold water (0 °C, 10 mL) and adjusted to pH 8-9 with saturated Na_2CO_3 solution. Then water was removed by rotary evaporator and product was finally obtained by column chromatography on silica gel.

*Workup for **4b**.* After completion of the reaction monitored by TLC, the solvent was removed and the residue was quenched with cold water (0 °C, 10 mL). Then water was removed by rotary evaporator and hydrochloride salt of the target was obtained by column chromatography on silica gel (product is not stable unless in hydrochloride salt form).

Procedure for one-pot pharmaceutical synthesis.

*Procedure for synthesizing idelalisib (**8a**).* In a 1000 mL round-bottomed flask with 50 g 6-hydroxypurine, 200 mL $SOCl_2$, 2.5 g DMAP, the mixture was heated to reflux. BTC/$SOCl_2$ solution (100 g BTC were dissolved in 200 mL of $SOCl_2$ was added dropwise. Then the reaction was monitored by TLC until complete exhaustion of 6-hydroxypurine. $SOCl_2$ was recovered by evaporation (recovered $SOCl_2$ 385 mL) to give a light yellow powder (6-chloroindole and DMAP hydrochloride) as crude intermediate. 74 g Et_3N and 100 mL ethanol were directly added to the intermediate, and the mixture was heated to reflux again, into which 110 g (S)-2-(1-aMinopropyl)-5-fluoro-3-phenylquinazolin-4(3*H*)-one (**7a**) was dripping under nitrogen protection. Stopped reaction when TLC showed complete

conversion of 6-chloroindole. Ethanol was removed under reduced pressure and 500 mL water was added. The aqueous mixture was then extract with ethyl acetate (1000 mL*3) and the organic layer was dried by Na_2SO_4. Crude product was obtained by removal of solvent from organic layer. Finally, recrystallization in ethanol to give the product.

*Procedure for synthesizing 6-benzylaminopurine (**8b**).* In a 1000 mL round-bottomed flask with 50 g 6-hydroxypurine, 200 mL $SOCl_2$, 2.5 g DMAP, the mixture was heated to reflux. BTC/$SOCl_2$ solution (100 g BTC were dissolved in 200 mL of $SOCl_2$ was added dropwise. Then the reaction was monitored by TLC until complete exhaustion of 6-hydroxypurine. $SOCl_2$ was recovered by evaporation (recovered $SOCl_2$ 385 mL) to give a light yellow powder (6-chloroindole and DMAP hydrochloride) as crude intermediate. 74 g Et_3N and 100 mL of ethanol were directly added to the intermediate, and the mixture was heated to reflux again, into which 43 g benzylamine (**7b**) was dripping under nitrogen protection. Stopped reaction when TLC showed complete conversion of 6-chloroindole. Ethanol was removed under reduced pressure and 500 mL water was added. The aqueous mixture was then extract with ethyl acetate (1000 mL*3) and the organic layer was dried by Na_2SO_4. Crude product was obtained by removal of solvent from organic layer. Finally, recrystallization in ethanol to give the product.

*Procedure for synthesizing kinetin (**8c**).* In a 1000 mL round-bottomed flask with 50 g 6-hydroxypurine, 200 mL of $SOCl_2$, 2.5 g of DMAP, the mixture was heated to reflux. BTC/$SOCl_2$ solution (100 g BTC were dissolved in 200 mL of $SOCl_2$ was added dropwise. Then the reaction was monitored by TLC until complete exhaustion of 6-hydroxypurine. $SOCl_2$ was recovered by evaporation (recovered $SOCl_2$ 388 mL) to give a light yellow powder (6-chloroindole and DMAP hydrochloride) as crude intermediate. 74 g Et_3N and 100 mL of ethanol were directly added to the intermediate, and the mixture was heated to reflux again, into which 39 g furfurylamine (**7c**) was dripping under nitrogen protection. Stopped reaction when TLC showed complete conversion of 6-chloroindole. Ethanol was removed under reduced pressure and 500 mL water was added. The aqueous mixture was then extract with ethyl acetate (1000 mL*3) and the organic layer was evaporated under reduced pressure. Finally, recrystallization in ethanol to give the product.

*Procedure for synthesizing 6-mercaptopurine (**8d**).* In a 1000 mL round-bottomed flask with 50 g 6-hydroxypurin, 200 mL of $SOCl_2$, 2.5 g of DMAP, the mixture was heated to reflux. BTC/$SOCl_2$ solution (100 g BTC were dissolved in 200 mL of $SOCl_2$ was added dropwise. Then the reaction was monitored by TLC until complete exhaustion of 6-hydroxypurine. $SOCl_2$ was recovered by evaporation (recovered $SOCl_2$ 391 mL) to give a light yellow powder (6-chloroindole and DMAP hydrochloride) as crude intermediate. 33 g thiocarbamide (**7d**) and 100 mL ethanol were directly added to the intermediate and then heated to reflux until the conversion of 6-chloropurine was complete (TLC monitoring). The mixture was poured into 200 mL 30% NaOH aqueous solution, to which acetic acid was added dropwise to deposit solid. Stop adding acetic acid when no more solid is formed. After filtration, the final product was recrystallized from ethanol.

ACKNOWLEDGMENTS

We thank department of education of Zhejiang province (educational reform and research project of higher educational 13th five-year plan No. jg20180426) for financial support.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

(1) Supplementary data for optimization of hypoxanthine chlorination; (2) Characterization of all products (3) NMR spectra of all products (PDF)

REFERENCES

(1) (a) Dubois. K. P.; Cochran. K. W; Thomson. J. F. Rodenticidal action of 2-chloro-4-dimethylamino-6-methylpyrimidine (castrix). *P. Soc. Exp. Biol. Med.* **1948**, *67*, 169-171. (b) Fakhraian, H.; Moghimi, A.; Ghadiri, H.; Dehnavi, M. A.; Sadeghi, M. Reinvestigation of Phase-Transfer-Catalyzed Chlorpyrifos Synthesis. *Org. Process Res. Dev*. **2004**, *8*, 680-684. (c): Zhang, Z. W.; Gao, Z. H.; Wang, Y.; Yuan, Y. H.; Dong, J.; Yue, T. L. Transformation products elucidation of for chlorfenuron in postharvest kiwifruit by time-of-flight mass spectrometry. *PLoS One.* **2017,** *12,* 1-15. (d) Calumpang, S. M. F.; Medina, M. J. B. Applicator exposure to Imidacloprid while spraying mangoes. *Bull. Environ. Contam. Toxicol*. **1996**, *57*, 697-704.

(2) (a) Lindner. I.; Stormann, H.; Wendtlandt, W. Toxicological investigation of 3-chloro-6-pyridazinylthioacetic acid-diethylamide and its effect on several enzymes. *Arzneim.-Forsch.* **1964**, *14*, 271-279. (b) Vassalli, J. D.; Belin, D. Amiloride selectively inhibits the urokinase-type plasminogen activator. *FEBS Lett.* **1987**, *214*, 187-191. (c) Löwenberg, B.; Pabst, T,; Maertens, Johan. T. Therapeutic value of clofarabine in younger and middle-aged (18-65 years) adults with newly diagnosed AML. *Blood*. **2017**, *129*, 1636-1645. (d) Janeba, Z.; Francom, P.; Robins, M. J. Efficient Syntheses of 2-Chloro-2'-deoxyadenosine (Cladribine) from 2'-Deoxyguanosine. *J. Org. Chem*. **2003**, *68*, 989-992. (e) Huang, W. S.; Liu, S.; Zou, D.; Thomas, M.; Wang, Y.; Zhou, T.; Romero, J.; Kohlmann, A.; Li, F. Discovery of Brigatinib (AP26113), a Phosphine Oxide-Containing, Potent, Orally Active Inhibitor of Anaplastic Lymphoma Kinase. *J. Med. Chem.* **2016**, *59*, 4948-4964.

(3) (a) Cole, J. E.; Jr; Gumprecht, W. H. Single pad thermal process for dyeing textile fibers. **1965**, U.S. Patent 3184282. (b) Mohamed, F. A.; Ali, N.; EL-Mohamedy, R. Evaluation of the antimicrobial activity for wool fibers dyed with new synthesized reactive dyes. *Int. J. Pharm. Sci. Rev. Res*. **2017**, *44*, 121-126. (c) Cardoso, V.; Rittmeyer, T.; Correa, R. J.; Breda, G. C.; Almeida, R. V.; Simoes, G.; de Franca, B. M.; de Azevedo, P. N.; Bello Forero, J. S. Photoactive cotton fabric: Synthesis, characterization and antibacterial evaluation of anthraquinone-based dyes linked to cellulose. *Dyes. Pigments.* **2019**, *161*, 16-23.

(4) (a) Manvar, A.; Shah, A. Microwave-assisted chemistry of purines and xanthines. An overview. *Tetrahedron*. **2013**, *69*, 8105-8127. (b) Chupakhin, O. N.; Charushin, V. N. Recent advances in the field of nucleophilic aromatic substitution of hydrogen. *Tetrahedron Lett*. **2016**, *57*, 2665–2672. (c) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. Advance in the directed metallation of azines and diazines (pyridines, pyrimidines, pyrazines, pyridazines, quinolines, benzodiazines and carbolines). Part 2: metallation of pyrimidines, pyrazines, pyridazines and benzodiazines. *Tetrahedron*. **2001**, *57*, 4489-1505.

(5) (a) Lee, D. H.; Jung, J. Y.; Jin, M. J. Highly active and recyclable silica gel-supported palladium catalyst for mild cross-coupling reactions of unactivated heteroaryl chlorides. *Green Chem*. **2010**, *12*, 2024-2029. (b) Kanchupalli, V.; Joseph, D.; Katukojvala, S. Pyridazine N-Oxides as Precursors of Metallocarbenes: Rhodium-Catalyzed Transannulation with Pyrroles. *Org. Lett.* **2015**, *17*, 5878-5881. (c) Saygili, N.; Batsanov, A. S.; Bryce, M. R. 5-Pyrimidylboronic acid and 2-methoxy-5-pyrimidylboronic acid: new heteroarylpyrimidine derivatives via Suzuki cross-coupling reactions. *Org. Biomol. Chem.*

2004, *2*, 852-857. (d) Kakad, S. P.; Thakare, S. S. Palladium catalyzed Suzuki reaction for synthesis of new trisubstituted quinazoline derivatives. *Heterocycl. Lett.* **2016**, *6,* 513-520.
(6) (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. The Stille reaction. *Organic Reactions* (Hoboken, NJ, United States), **1997**, *50*. (b) Lavecchia, G.; Berteina-Raboin, S.; Guillaumet, G. Selective bifunctionalization of pyrido[2,3-d]pyrimidines in positions 2 and 4 by SNAr and palladium-catalyzed coupling reactions. *Tetrahedron Lett*. **2005**, *46*, 5851-5855. (c) Lee, D. H.; Taher, A.; Ahn, W. S.; Jin, M. J. Room temperature Stille cross-coupling reaction of unreactive aryl chlorides and heteroaryl chlorides. *Chem. Commun.* **2010**, *46*, 478-480.
(7) (a) Iyer, S.; Kulkarni, G. M.; Ramesh, C. Mizoroki-Heck reaction, catalysis by nitrogen ligand Pd complexes and activation of aryl bromides. *Tetrahedron Lett*. **2004**, *60*, 2163-2172. (b) Sharma, N.; Asthana, M.; Kumar, R.; Mishra, K.; Singh, R. M. rac-BINAP-$PdCl_2$ catalyzed Heck reactions of 3-formylquinolin-2-yl chlorides with methyl acrylate. Synthesis of methyl 3-(3-formylquinolin-2-yl) acrylates. *Tetrahedron Lett.* **2014**, *55*, 2348-2351. (c) Lee, D. H.; Taher, A.; Hossain, S.; Jin, M. J. *Org. Lett*. **2011**, *13*, 5540-5543. (d) Chen, L. Y.; Rangan, S.; Li, J.; Jiang, H. F.; Li, Y. W. A molecular Pd(II) complex incorporated into a MOF as a highly active single-site heterogeneous catalyst for C-Cl bond activation. *Green Chem*. **2014**, *16*, 3978-3985.
(8) (a) Boully, L.; Darabantu, M.; Turck, A.; Ple, N. Aryl-aryl bonds formation in pyridine and diazine series. Diazines. Part 41. *J. Heterocycl. Chem*. **2005**, *42*, 1423-1428. (b) Dhital, R. N.; Kamonsatikul, C.; Somsook, E.; Sakurai, H. Bimetallic gold-palladium alloy nanoclusters: an effective catalyst for Ullmann coupling of chloropyridines under ambient conditions. *Catal. Sci. Technol.* **2013**, *3*, 3030-3035. (c) Bégouin, J. M.; Gosmini, C. Cobalt-Catalyzed Cross-Coupling Between In Situ Prepared Arylzinc Halides and 2-Chloropyrimidine or 2-Chloropyrazine. *J. Org. Chem*. **2009**, *74*, 3221-3224. (d) Xi, Z. X.; Zhou, Y. B.; Chen, W. Z. Efficient Negishi Coupling Reactions of Aryl Chlorides Catalyzed by Binuclear and Mononuclear Nickel-N-Heterocyclic Carbene Complexes. *J. Org. Chem.* **2008**, *73*, 8497-8501. (e) Cherney, A. H.; Hedley, S. J.; Mennen, S. M.; Tedrow, J. S. Xantphos as a Branch-Selective Ligand for the Acyclic sec-Alkyl Negishi Cross-Coupling of Heteroaryl Halides. *Organometallics*. **2019**, *38*, 97-102. (f) Topchiy, M. A.; Dzhevakov, P. B.; Rubina, M. S.; Morozov, O. S. S. Solvent-Free Buchwald-Hartwig (Hetero)arylation of Anilines, Diarylamines, and Dialkylamines Mediated by Expanded-Ring N-Heterocyclic Carbene Palladium Complexes. *Eur. J. Org. Chem.* **2016**, 1908-1914. (g) Yang, L. R.; Bian, H. Y.; Mai, W. P.; Mao, P. Synthesis of tetrahydropyrimidinium salts and their in situ catalytic activities towards the Buchwald-Hartwig amination reaction under microwave irradiation. *Turk. J. Chem*. **2015**, *39*, 121-129. (h) Lundgren, R. J.; Sappong-Kumankumah, A.; Stradiotto, M. A Highly Versatile Catalyst System for the Cross-Coupling of Aryl Chlorides and Amines. *Chem. Eur. J*. **2010**, *16*, 1983-1991. (i) Hosseini-Sarvari, M.; Razmi, Z. Highly active recyclable heterogeneous Pd/ZnO nanoparticle catalyst: sustainable developments for the C-O and C-N bond cross-coupling reactions of aryl halides under ligand-free conditions. *RSC Adv.* **2014**, *4*, 44105-44116. (j) Zhang, Q.; Wang, D. Q.; Wang, X. Y.; Ding, K. (2-Pyridyl)acetone-Promoted Cu-Catalyzed O-Arylation of Phenols with Aryl Iodides, Bromides, and Chlorides. *J. Org. Chem*. **2009**, *74*, 7187-7190. (k) Goriya, Y.; Ramana, C.V. The [Cu]-catalyzed SNAR reactions: direct amination of electron deficient aryl halides with sodium azide and the synthesis of arylthioethers under Cu (II)-ascorbate redox system. *Tetrahedron* **2010**, *66*, 7642-7650.
(9) (a) Masuda, H; Mihara, S. Synthesis of alkoxy-, (alkylthio)-, phenoxy-, and (phenylthio)pyrazines and their olfactive properties. *J. Agric. Food. Chem.* **1986**, *2*, 377-381. (b) Ohta, A; Akita, Y; Hara, M. Syntheses and reactions of some 2, 5-disubstituted pyrazine monoxides. *Chem. Pharm. Bull*. **1979**, *27*, 2027-2041. (c) Sun, R. F.; Zhang, Y. L.; Bi, F. C.; Wang, Q. M. Design, synthesis, and bioactivity study of novel benzoylpyridazyl ureas. *J. Agric. Food. Chem.* **2009**, *57*, 6356-6361. (d) Katrusiak, A.; Katrusiak, A. Polymorph-specific chlorination of maleic-hydrazide. *J. Mol. Struct*. **2003**, *647*, 203-210. (g) Artueur, H; Bonn, G. Process for the preparation of chloropyrimidines. U.S. Patent 5525724 11, Jun, 1996. (h) Zhang, Z. Y.; Wallace, M. B.; Feng, J.; Stafford, J. A. Design and synthesis of pyrimidinone and pyrimidinedione inhibitors of dipeptidyl peptidase IV. *J. Med. Chem*. **2011**, *54*, 510-524. (i) Deng, X. H.; Roessler, A.; Brdar I. Direct, Metal-Free Amination of Heterocyclic Amides/Ureas with NH-Heterocycles and N-Substituted Anilines in $POCl_3$. *J. Org. Chem.* **2011**, *76*, 8262-8269.
(10) (a) Gabriel, S. Notes Over Bromo Dihydro Uracil. *Chem. Ber*. **1905**, *38*, 1689–1991. (b) Whittaker, N.; Jones, T. S. G. New synthesis and the chemical properties of 5-aminopyrimidine. *J. Chem. Soc*. **1951**, 1565-1570.
(11) (a) Carpenter, S. R.. Phosphorus control is critical to mitigating eutrophication. *P. Natl. Acad. Sci. USA*. **2008**, 105, 11039-11040. (b) Rotta, E.; Minkea, R.; Steinmetzb, H. Removal of phosphorus from phosphonate-loaded industrial wastewaters via precipitation/flocculation. *J. Water Process Eng*. **2017**, *17*, 188-196. (c) Yang, L. Y.; Sheng, M.; Zhao, H. H.; Qian, M. C.; Chen, X. K.; Zhuo, Y. K.; Cao, K. M.. Treatment of triethyl phosphate wastewater by Fenton oxidation and aerobic biodegradation. *Sci. Total Environ.* **2009**, *678*, 821-829. (d) Bunce, J. T.; Ndam, E.; Ofiteru, R. D.; Moore, A.; Graham, D. W. A review of phosphorus removal technologies and their applicability to small-scale domestic wastewater treatment systems. *Front. Env. Sci.* **2018**, *6*, 1-15. (e) McComas, C, McKinley, D. Reduction of phosphorus and other pollutants from industrial dischargers using pollution prevention. *J. Clean. Prod*. **2008**, *16*, 727-733. (f) Wang, H.; Shen, Y. J.; Sun Z. H. Large-scale solvent-free chlorination of hydroxy-pyrimidines, -pyridines, -pyrazines and -amides using equimolar $POCl_3$. *Molecules*. **2012**, *17*, 4533-4544. (g) Sun, Z. H.; Wang, H.; Wen, K.; Li, Y. Solvent-Free or Low-Solvent Large-Scale Preparation of Chloropyrimidine and Analogues. *J. Org. Chem*. **2011**, *76*, 4149-4153.
(12) (a) Kong, X. M.; Li, J. H.; Zhou, H. Y.; Liu, S. N.; Zhang, Z. P.; Wang, W.; Deng, Q. S.; Zhou, J. F.; Zheng, L.; Zhu, Z. Q.; Li, Q. H.; Yang, A. B. One sulfur-containing hydrogen chloride purification treatment method. **2010**, CN 101823694 A. (b) Cho, W.; Cho, H.; Lee, C. S. Synthesis of new bis(amidine)-cobalt catalysts and their application to styrene polymerization. *Organometallics.* **2014**, *33*, 1617-1622. (c) Romer, D. R. Synthesis of 2, 3-dichloroquinoxalines via Vilsmeier reagent chlorination. *J. Heterocycl. Chem.* **2009**, *46*, 317-319. (d) Shen, C.; Wang, L. F.; Wen, M. Synthesis of Benzimidazo [1, 2-c]quinazolines via Metal-Free Intramolecular C-H Amination Reaction. *Ind. Eng. Chem. Res.* **2016**, *55,* 3177-3181. (e) Tago, T.; Furumoto, S.; Okamura, N.; Harada, R.; Yoichi, I.; Arai, H.; Yanai, K.; Iwata, R.; Kudo, Y. Synthesis and preliminary evaluation of 2-arylhydroxyquinoline derivatives for tau imaging. *J. Label Compd. Radiopharm*. **2014**, *57*, 18-24. (f) Chun, K.; Park, J. S.; Lee, H. C. Synthesis and evaluation of 8-amino-[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one derivatives as glycogen synthase kinase-3 (GSK-3) inhibitors. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 3983-3987.
(13) (a) Chen, Z. W; Jiang, L.; Su, W. K.; Xu, Z. J. An efficient method for preparation of acyl chlorides and symmetrical anhydrides from carboxylic acids with BTC/DMF. *J. Chem. Soc. Pak.* **2012**, *34*, 1003-1006. (b) Liu, J.; Kimmel, K.; Dao, K.; Liu, Y.; Qi, M. Identification and Elimination of an Unexpected Catalyst Poison in Suzuki Coupling. *Org. Process Res. Dev.* **2018**, *22*, 111-116. (c) Ayala, C. E.; Villalpando, A.; Nguyen, A. L.; McCandless, G. T.; Kartika, R. Chlorination of Aliphatic Primary Alcohols via Triphosgene-Triethylamine Activation. *Org. Lett*. **2012**, *14*, 3676-3679. (d) Villalpando, A.; Ayala, C. E.; Watson, C. B.; Kartika, R. Triphosgene-Amine Base Promoted Chlorination of Unactivated Aliphatic Alcohols. *J. Org. Chem.* **2013**, *78*, 3989-3996. (e) Cotarca, L.; Geller, T.; Répási, J. Bis(trichloromethyl)carbonate (BTC, Triphosgene): A Safer Alternative to Phosgene. *Org. Process Res. Dev.* **2017**, *21*, 9, 1439-1446.
(14) (a) Doležal, K.; Popa, I.; Kryštof, V.; Spíchal, L.; Fojtíková, M.; Holub, J.; Lenobel, R.; Schmülling, T.; and Strnad, M. Preparation and

biological activity of 6-benzylaminopurine derivatives in plants and human cancer cells. *Bioorg. Med. Chem.* **2006**, *14*, 875-884. (b) Sariri, R.; Khalili, G. Synthesis of Purine Antiviral Agents, Hypoxanthine and 6-Mercaptopurine. *Russ. J. Org. Chem.* **2002**, *38*, 1053-1055. (c) Wang, X. B.; Han, C.; Wu, K. Q.; Luo, L. Design, synthesis and ability of non-gold complexed substituted purine derivatives to inhibit LPS-induced inflammatory response. *Eur. J. Med. Chem*. **2018**, *149*, 10-21. (d) Liu, J.; Huang, Y.; Cheng, X. H.; Liu X. K. A Novel Method of Preparing (S)-5-Fluoro-3-phenyl-2-[1-(9H-purin-6-ylamino)propyl]-3H-quinazolin-4-one. *Org. Prep. Proced. Int.* **2016**, *48*, 337-341. (e) Ren, P.; Martin, M.; Isbester, P.; Lane, B. S. Processes for preparing isoquinolinones and solid forms of isoquinolinones. **2012**, July 19, WO2012097000A1. (f) Pei, J. Y.; Li, J.; Xie, Y.; Weng, J. S. Large-scale synthesis of (E)-4-amino-2-methylbut-2-en-1-ol: key building block for the synthesis of trans-zeatin. *Asian J. Chem.* **2014**, *26*, 8155-8157.

(15) Jain, M. L.; Tsao, Y. P.; Ho, N. L.; Cheng, J. W. A Facile Synthesis of [N1,NH_2-$^{15}N_2$]-, [N3,NH_2-$^{15}N_2$]-, and [N1,N3,NH_2-$^{15}N_3$]-Labeled Adenine. *J. Org. Chem.* **2001**, *66*, 6472-6475.

(16) (a) Maes, B. U. W.; Verbeeck, S.; Verhelst, T.; Ekomié, A.; Wolff, N.; LefÀvre, G.; Mitchell, E. A.; Jutand, A. Oxidative Addition of Haloheteroarenes to Palladium(0): Concerted versus SNAr-Type Mechanism. *Chem. Eur. J*. **2015**, *21*, 7858-7865. (b) Fruman, D. A.; Cantley, L. C. Idelalisib–A PI3Kδ inhibitor for B-cell cancers. *N. Engl. J. Med*. **2014**, *370*, 1061-1062. (c) Wu, M.; Akinleye, A.; Zhu, X. Novel agents for chronic lym-phocytic leukemia. *J. Hematol. Oncol*. **2013**, *6*, 36. (d) Zhang, Y. L.; Sun, T. M. Idelalisib (in Chinese). Chin. *J. Med. Chem*. **2015**, *25*, 78. (e) Spreitzer, H. Neue Wirkstoffe– Ibrutinib und Idelalisib (in German). *Österreichische Apothekerzeitung*. **2013**, *10*, 34. (f) Bendich, A.; Russell, Percy J.; Jr.; Fox, J. J. The synthesis and properties of 6-chloropurine and purine. *J. Amer. Chem. Soc.* **1954**, *76*, 6073-6077. (g) Ubiali, D, Morelli, C. F.; Rabuffetti, M.; Cattaneo, G.; Serra, I.; Bava-ro, T.; Albertini, A. M.; Speranza, G. Substrate specificity of a purine nucleoside phosphorylase from aeromonas hydrophila toward 6-substitutedpurines and its use as a biocatalyst in the synthesis of the corresponding ribonucleosides. *Curr. Org. Chem*. **2015**, *19*, 2220-2225.

(17) Huang, L. K.; Cherng, Y. C.; Cheng, Y. R.; Jang, J. P.; Chao, Y. L.; Cherng Y. J. A. An efficient synthesis of substituted cytosines and purines under focused microwave irradiation. *Tetrahedron* **2007**, *63*, 5323-5327.

(18) Wan, Z. K.; Wacharasindhu, S.; Binnun, E.; Mansour, T. An efficient direct amination of cyclic amides and cyclic ureas. *Org. Lett.* **2006**, *8*, 2425-2428.

(19) Bryant, C. P.; Harmon, R. E. Aminomethylation and hydroxymethylation of purine-6(1*H*)-thione and 6-alkylthiopurines. *J. Med. Chem.* **1967**, *10*, 104-106.

(20) (a) Moshood, O.; Ganiu, Alexander H.; Cleveland, Jarrod L.; Kartika, R. Triphosgene and DMAP as mild reagents for chemoselective dehydration of tertiary alcohols. *Org. Lett*. **2019**, *21*, 5611-5615. (b) Mirza, A.; Saputra, Ly Ngo.; Kartik, R. Synthesis of vinyl chlorides via triphosgene−pyridine activation of ketones. *J. Org. Chem*. **2015**, *80*, 8815-8820.

For Table of Contents Only