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Article

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A One-Pot Cascade Heterocyclization of γ- and β-Ketomalononitriles to 2,4-diChloro Substituted Pyrano[2,3-*d*]Pyrimidines and Furo[2,3-d]Pyrimidines Mediated by Triphosgene and Triphenylphosphine Oxide

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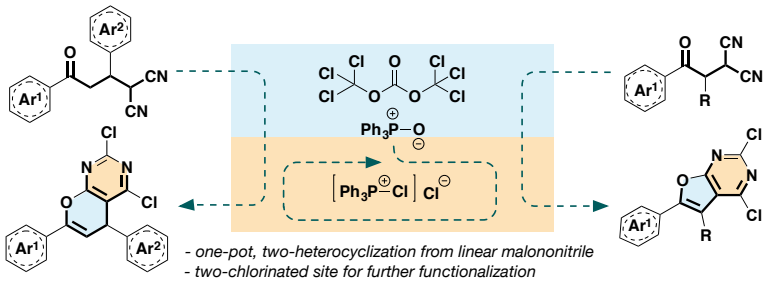
Abstract

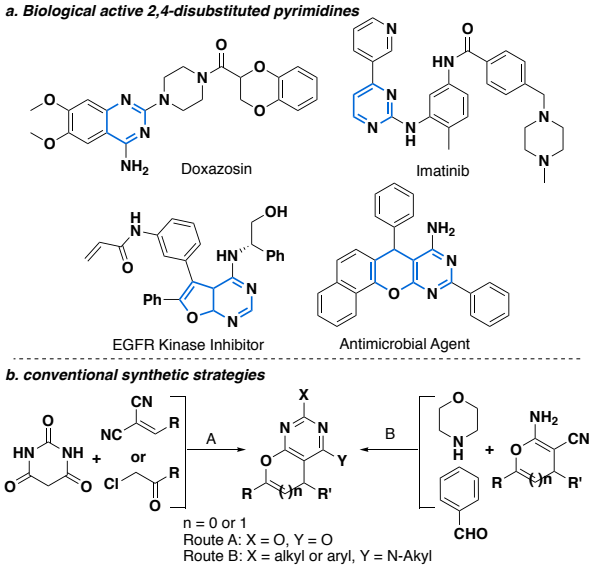
A one-pot cascade heterocyclization strategy had been developed for the synthesis of 2,4-dichloro substituted pyrano[2,3-*d*]pyrimidines and furo[2,3-*d*]pyrimidines from linear γ- and β-ketomalononitriles using triphosgene and triphenylphosphine oxide. The reaction afforded synthetic useful products with moderate to good yields bypassing the conventional harsh conditions of chlorination. The mechanistic study revealed the reaction underwent a non-isocyanate route, and the second step may conduct in a triphenylphosphine oxide-catalyzed manner.



Introduction

2,4-disubstituted pyrimidines are important pharmacophore and synthetic motif, and have already been embedded in several antihypertensives (doxazosin, prazosin, et al.) and tyrosine kinase inhibitors (imatinib, dasatinib, et al.).[1] Among them, the 2,4-disubstituted pyrano[2,3-*d*]pyrimidines and furo[2,3-*d*]pyrimidines have shown their biological activities such as antimicrobial, antioxidant, and anticancer (Scheme 1a).[2] Despite the wide interest in these compounds, the synthetic methods remain limited. One of the most popular routes employs the nucleophilic attack from barbituric acid to 2-methylenemalononitriles or α-chloroketones (Scheme 1b, Route A),[2b,2g,3] providing pyrimidiones for rapid reductive amination. Meanwhile, another

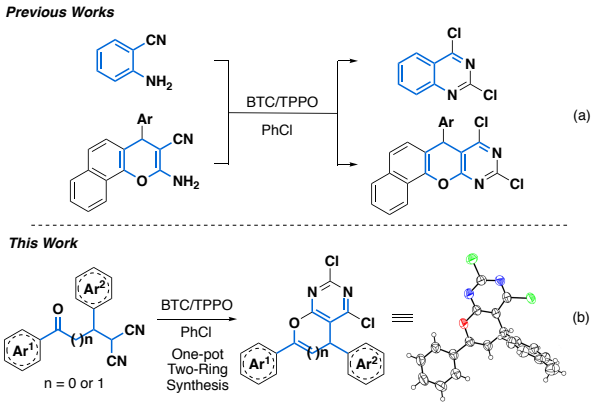
prevailing route starts from the 2-amino-pyran(or furan)-3-carbonitriles affording 2,4-disubstituted products for biological assessment directly (Scheme 1b, Route B).[2a,2j,4] Pd-catalyzed 5-*endo-dig* cyclization also provides a way to access the furo[2,3-*d*]pyrimidines.[5] Hitherto, abundant compounds have been synthesized using these strategies, however, the relative narrow structural diversity at 2,4-position constrained their further investigation. Chloride substituted at 2,4-positions have been proved as a useful method, however, the harsh conditions are usually required to obtain those synthetic useful substrates.[6] Thus, it's highly desired for a novel protocol affording pyrano[2,3-*d*]pyrimidines and furo[2,3-*d*]pyrimidines with 2,4-dichloro substituted, which may benefit the following functionalization.



Scheme 1. Biological active 2,4-disubstituted pyrimidines and conventional synthetic route of 2,4-disubstituted pyrano[2,4-*d*]pyrimidines.

Triphosgene, also known as bis(trichloromethyl)carbonate (BTC) or solid phosgene, has been considered as a safe and easy-handled alternative of highly toxic phosgene. The reagent has been used in various situations including chlorination, acylation, and cyclization.[7] During our continuous effort expanding the chemistry of BTC,[7c,8] an eco-friendly method has been developed transforming notorious triphenylphosphine oxide (TPPO) to a versatile chlorination reagent triphenylphosphine dichloride (TPPDC).[9] Previously, the system had been applied in the construction of 2,4-dichloro benzopyrimidines and benzochromeno[2,3-*d*]pyrimidines (Scheme 2a),[10] and a similar diphosgene/acetonitrile strategy had also been employed in the synthesis of heterocycle-fused 2,4-dichloro-pyrimidines.[11] Despite the success, the stepwise synthesis of 2-amino-3-cyano heterocycles still intrigued us about the possibility to furnish 2,4-dichloropyrimidines from their precursor ketomalonitriles directly.[12] Fortunately, during the efficacy evaluation of different BTC

systems, this envisioned transformation was achieved by an accidental misoperation, where (*E*)-2-(3-oxo-1-phenyl-3-(*p*-tolyl)prop-1-en-1-yl)malononitrile was added into the BTC/TPPO mixture before heating. The structure of the product was carefully identified and supported by the subsequent single-crystal X-ray diffraction (Scheme 2b). Herein, we wish to uncover our latest work about the direct construction from γ-ketomalononitriles to 2,4-dichloro pyrano[2,3-d]pyrimidines, and its further expansion to 2,4-dichloro furo[2,3-*d*]pyrimidines. The mechanistic investigation implicated the reaction was highly sensitive to the substrate addition temperature, and the classical isocyanate-mechanism may be absent in this transformation. Thus, a tentative non-isocyanate mechanism was proposed based on the temperature-sensitive base-free pathway of BTC/TPPO to TPPDC.



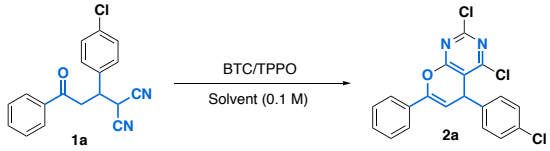
Scheme 2. The one-pot strategies for the 2,4-dichloro pyrimidines. ORTEP diagram with 50% ellipsoid probability for non-H atoms of the compound of to **2j** (CCDC number 1562782).

Result and Discussion

Synthetic study of 2,4-dichloro pyrano[2,3-d]pyrimidines. The transformation of 2-(1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)malononitrile (**1a**) to 2,4-dichloro-5-(4-chlorophenyl)-7-phenyl-5H-pyrano[2,3-*d*]pyrimidine (**2a**) was chosen as model reaction for optimization, where the selected results was summarized in Table 1. At the commencement, the usage of BTC/TPPO system and its combination ratio were examined. According to our previous works,[10b] optimal ratio of BTC/TPPO was 1/3, which showed a similar result in this reaction (Table 1, entries 1-4). Increasing the usage of BTC/TPPO gave better results (Table 1, entries 5-7), and the optimal ratio of was found to be 1/1/3. Attempts failed to use a catalytic amount of TPPO as previous reported (Table 1, entries 8, 9),[9b,10a] which indicated the necessity of the large amount TPPO. Fortunately, the product could be separated conveniently by *n*-hexane extraction, and the TPPO could be recovered by recrystallization from ethanol efficiently.[13] Subsequent screening of solvents didn't offer better yields (Table 1, entries 10-14). Although toluene also gave an acceptable result, the reaction time was

prolonged dramatically to over 12 hours. Besides, the yield increased with higher temperature (Table 1, entries 15-17), but the refluxing didn't give any superior result. Further tracking of reaction process found the transformation ended at 1.5 hours (Table 1, entry 18).

Table 1. Optimization of Reaction Condition. [a]



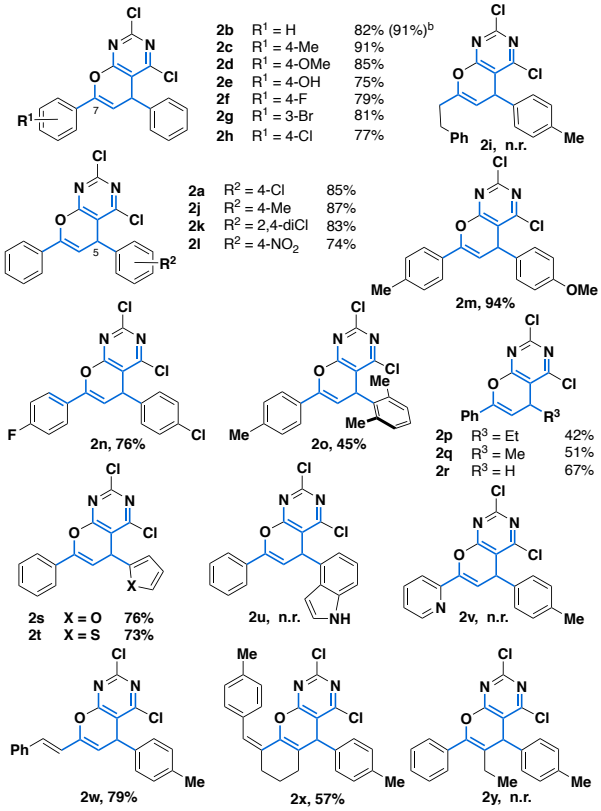
entry	Ratio **1a** : BTC : TPPO	Solvent	T/°C	time/hr	% yield [b]
1	1 : 0.34 : 1.00	PhCl	110	5	45
2	1 : 0.34 : 0.34	PhCl	110	5	n.d.
3	1 : 0.34 : 0.67	PhCl	110	5	10
4	1 : 0.34 : 1.34	PhCl	110	5	44
5	1 : 0.67 : 2.00	PhCl	110	5	71
6	1 : 1.00 : 3.00	PhCl	110	5	85
7	1 : 1.34 : 4.00	PhCl	110	5	85
8	1 : 1.00 : 0.20	PhCl	110	24	trace
9	1 : 1.00 : 0.30	PhCl	110	24	trace
10	1 : 1.00 : 3.00	CH_2Cl_2	40	24	n.d.
11	1 : 1.00 : 3.00	$C_2H_4Cl_2$	80	24	65
12	1 : 1.00 : 3.00	2-MeTHF	80	24	50
13	1 : 1.00 : 3.00	Toluene	110	12	80
14	1 : 1.00 : 3.00	Dioxane	110	16	75
15	1 : 1.00 : 3.00	PhCl	80	5	72
16	1 : 1.00 : 3.00	PhCl	100	5	80
17	1 : 1.00 : 3.00	PhCl	131	5	84
18	**1 : 1.00 : 3.00**	**PhCl**	**110**	**1.5**	**85**

[a] Reaction conditions unless specified otherwise: BTC and TPPO in solvent (0.1 M) was premixed under ice-bath, and stirred at room temperature for 30 min. Then, **1a** was added and the mixture was heated to the specified temperature. [b] isolated yield based on **1a**.

With optimal condition established, a series of 2-(3-oxo-propyl)malononitriles was exposed to the standard condition, and the results were presented in Table 2. Firstly, the substitution effect was tested at 7 and 5 positions of pyrano-ring. For phenyl substituted at 7 position, the electron-donating substitutions (**2c-e**) gave better results than their electron-withdrawing counterpart (**2f-h**), where the lower electron density retarded the enolate's nucleophilic attack to nitrile group. Interestingly, nucleophilic phenolic group (**1e**) was also tolerated with a slight drop in yield, which prone to dimerize under BTC systems.[7a] Unfortunately, 2-phenylethyl at 7 position (**2i**) didn't react under this condition indicating the alkyl group may not suitable for this position. On the other side, the substitution effect at 5-phenyl group was not prominent, and similar yields

were obtained comparing with unsubstituted ones (**2a**, **j-n**). However, the steric hindrance at this site may cause significant decline on the outcomes, where a dramatically drop in yield was found using the 2,6-dimethylphenyl substrate (**2o**). 5-Ethyl and methyl derivatives both afforded desired products (**2p-q**) with moderate yields, however, much-hindered *n*-heptyl and benzyl failed in the tests. Besides, 5-unsubstituted substrate also gave acceptable result of 67%. Subsequent tests of furyl and thienyl substrate (**1s**, **t**) showed both heterocycles at 5-position survived under the standard condition, affording the corresponding product with a moderate yield of 76% and 73%, respectively. However indolyl or pyridyl substrates (**1u**, **v**) didn't provide corresponding products.[14] Cinnamyl derived substrate (**1w**) with internal double bond proceed smoothly, while cyclohexanone derived one (**1x**) also survived. Additional attempts failed to install other groups at 6-position including **2y**. The scalability of this protocol was also examined at 20 mmol using the model reaction (**1a** to **2a**), which afforded a good yield of 91% within 3 hours with 95% recovery of TPPO.

Table 2 Substrate scope of 2,4-dichloro pyrano[2,3-*d*]pyrimidines. [a]

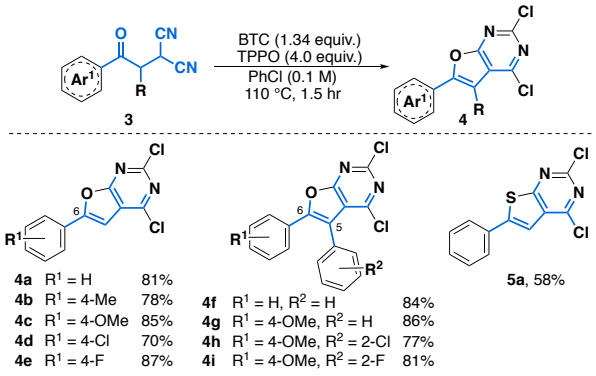


[a] Reaction conditions unless specified otherwise: BTC (1.0 mmol) and TPPO (3.0 mmol) in chlorobenzene (0.1 M) was premixed under ice-bath, and stirred at room temperature for 30 min. Then, **1** (1.0 mmol) was added and the mixture was heated to the 110 °C. Isolated yield based on **1**. [b] 20 mmol scale reaction. n.r. = no reaction.

Synthetic study of 2,4-dichloro furo[2,3-d]pyrimidines. After the investigation of one-pot synthesis of 2,4-dichloro pyrano[2,3-*d*]pyrimidines, we wondered if the method could be further introduced into the

preparation of 2,4-dichloro furo[2,3-*d*]pyrimidine derivatives. Fortunately, the model substrate 2-(2-oxo-2-phenylethyl)malononitrile **3a** transformed to 2,4-dichloro-6-phenylfuro[2,3-*d*]pyrimidine **4a** with a yield of 62% under the same condition. After a simple optimization, the yield was improved to 81% with the ratio of **3a**/BTC/TPPO of 1/1.34/4. Then, a preliminary substrate scope test was performed (Table 3). Both electron-donating and withdrawing substitutes on the 6-aryl group (**4b and c**) gave acceptable yields (**4b-e**). 5,6-diaryl substituted products could also be synthesized using the protocol(**4f-i**) where a slight drop in yields was found from the electron-withdrawing group on 5-position. Noteworthy, the 2,4-dichloro-6-phenylthieno[2,3-*d*]pyrimidine (**5a**) could also be obtained with a moderate yield, which has also been investigated in a series anticancer biological assessment.[15]

Table 3 Substrate scope of 2,4-dichloro furo[2,3-*d*]pyrimidines. [a]

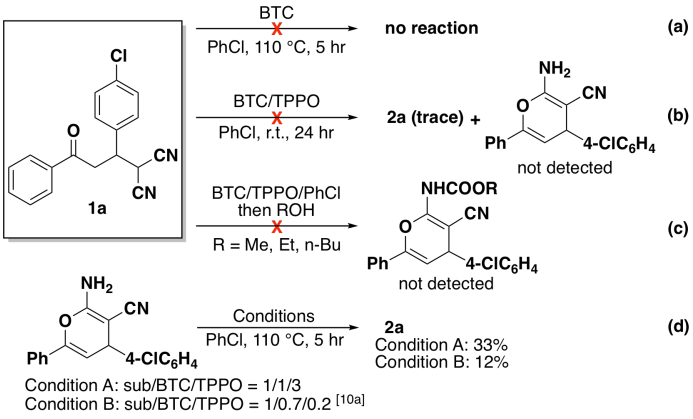


[a] Reaction conditions unless specified otherwise: BTC (1.34 mmol) and TPPO (4.0 mmol) in chlorobenzene (0.1 M) was premixed under ice-bath, and stirred at room temperature for 30 min. Then, **1** (1.0 mmol) was added and the mixture was heated to the 110 °C. Isolated yield based on **1**.

Mechanistic Study. Although the substrate examination gave satisfying results, the usage of 3.0 equivalent of TPPO still intrigued us to investigate the reason for its necessity. Previously, an isocyanate-based mechanism has been proposed by us and others.[10-11] However, when rescrutinizing the work of benzochromeno[2,3-*d*]pyrimidines,[10a] the failure of TPPO catalysis could hardly be explained by this mechanism as well as the protocol presented here. Thus, several control experiments were conducted for insight (Scheme 3). Firstly, the substrate **1a** was treated by BTC from low to an elevated temperature, where the substrate remained intact without any trace of chlorination (Scheme 3a). Then, **1a** was added to the activated BTC/TPPO mixture at room temperature and stirred for 24 hours without heating. Although the substance consumed rapidly in 30 minutes, no product or theoretical intermediate 2-amino-4H-pyran-3-carbonitrile was detected (Scheme 3b). The only information obtained from the TLC plate was a series inseparable high polarity spots. To avoid the possible consumption of intermediate generated, the ratio of **1a**/BTC/TPPO was reduced to 1/0.34/1, which

still gave an inseparable mixture with a little unconsumed substrate. Next, attempts failed to capture the isocyanate intermediate using alcohols, where no corresponding carbamates were detected (Scheme 3c).[16] Treating 2-amino-4-(4-chlorophenyl)-6-phenyl-4H-pyran-3-carbonitrile with the standard condition only gave a much lower yield (33%) than its linear precursor (Scheme 3d, Condition A). And an extremely low yield (12%) was obtained under our previous TPPO-catalytic system, which indicated the reaction should be conducted from linear substrate directly.

Scheme 3 Control Experiments



Subsequently, the temperature of substrate addition was carefully examined (Figure 1). Interestingly, a dramatic decrease in yield was observed during temperature progressing. Noticeably, addition at 20 minutes (after 10 minutes stabilizing at 110 °C) gave nearly no product after 24 hours' heating, and 75% of the substrate was recovered from the reaction.

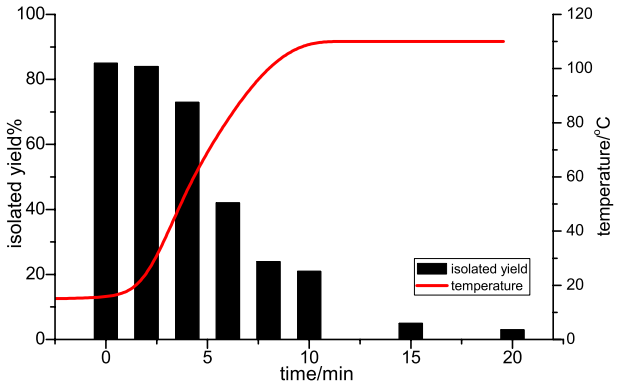
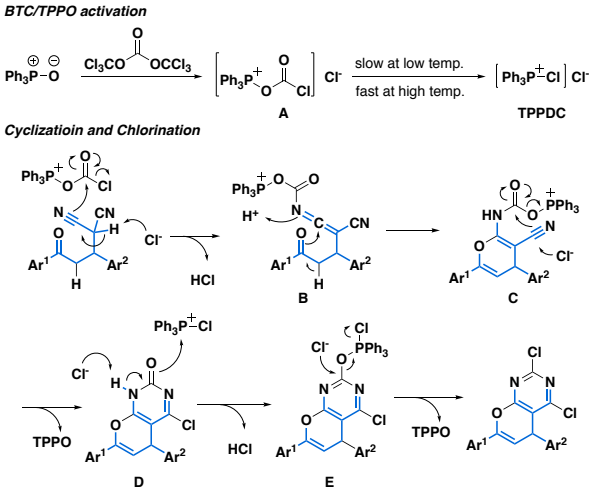


Figure 1 Experiment of adding substrate at different temperature (Black Column: Isolated yields based on **1a**; Red curve: average temperature at the time). Detailed data: 0 min, ca. 15 °C (before heating), 85% yield; 2 min, ca. 23°C, 84% yield; 4 min, ca. 40 °C, 73% yield; 6 min, ca. 75 °C, 42% yield; 8 min, ca. 85°C, 24% yield; 10 min, ca. 110 °C, 21% yield; 15 min, 110 °C, 5% yield; 20 min, 110°C, 3% yield (75% recovery of **1a**).

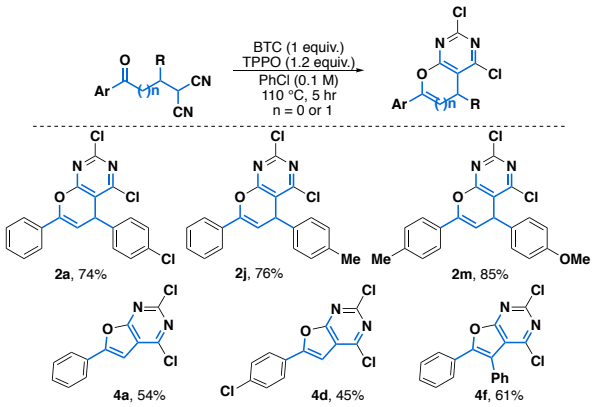
These experiments and optimization data above implied that: 1) **BTC and TPPDC cannot trigger the first heterocyclization**, and 2) **the activated BTC/TPPO mixture may form a low-temperature species before the TPPDC formation by CO_2 extrusion under high temperature**. 3) **This low-temperature species is responsible for the consumption of substrate giving a highly active or high polarity intermediate**, 4) and **TPPDC only participates the final step to afford products.** The signal of the low-temperature species and corresponding intermediate were detected by the ^{31}P-NMR study (See Supporting Information for more details). Besides, 5) **a base-free BTC/TPPO system could generate TPPDC under high temperature**,[10b] thus the formation of 2,4-dichloropyrimidine motif may undergo catalytic manner. However, due to the failure of catalysis, 6) **the first step of heterocyclization may afford an intermediated embedded a triphenylphosphine oxide molecule, rather than previously proposed 2-amino-4H-pyran-3-carbonitrile based on the isocyanate intermediates**.

Thus, based on the well-established mechanism of BTC activation[9-10] and the inference above, a plausible mechanism was proposed in scheme 4. After the mixture of BTC and TPPO, the nucleophilic attack from TPPO to BTC generates the ((chlorocarbonyl)oxy)triphenylphosphonium chloride (**A**) as low-temperature species during the activation step (30 min string at room temperature). After the substrate addition, the deprotonation occurs at more acidic malononitrile's methenyl position rather than α-hydrogen of the carbonyl group, which is then captured by **A** affording intermediate (**B**). Subsequently, the nucleophilic attack from enolate to C=N bond forms the first pyrano-ring (**C**). Then, with the temperature progressing, TPPDC is generated from excessive **A** by CO_2 extrusion. The closure of pyrimidine ring is then triggered by chloride's nucleophilic attack on the cyano group, and the cascade electron transfer is captured by TPPDC. Finally, the product is afforded by S_NAr mechanism replacing oxygen atom by chloride anion.

Scheme 4. Proposed non-isocyanate mechanism.



Based on this mechanism, the second step should be a TPPO-catalyzed procedure. However, during the reaction, TPPO detached from the intermediate was then participated in the transformation to TPPDC, which makes the overall reaction worked in a non-catalytic manner. To ensure this hypothesis, the ratio of 1/1/1.2 was tested for 6 substrates. Generally, the desired products were obtained within 5 hours, while an average drop of 10% for **2** and 25% for **4** was observed, respectively (Scheme 5). This higher sensitivity of 2-(2-oxo-ethyl)malononitrile substrates to mixture concentration matched well with higher concentration requirement of **A**. Thus, the over usage of TPPO in this reaction was supposed to facilitate the first heterocyclization. Besides, it's believed that previous synthesis of benzochromeno[2,3-*d*]pyrimidine may share the similar mechanism, where substoichiometric data also consisted with this hypothesis (55% yield for substrate/BTC/TPPO=1/1/1, and 68% yield for 1/1/2).[10b]



Scheme 5. Reaction tests using a reduced ratio of 1/1/1.2. Reaction conditions unless specified otherwise: BTC (1.0 mmol) and TPPO (1.2 mmol) in chlorobenzene (0.1 M) was premixed under ice-bath, and stirred at room temperature for 30 min. Then, **1** (1.0 mmol) was added and the mixture was heated to the 110 °C. Isolated yield based on **1**.

Conclusion

In the work presented, a one-pot direct construction of 2,4-dichloro pyrano[2,3-*d*]pyrimidines and furo[2,3-*d*]pyrimidines from γ- and β-ketomalononitriles had been achieved by a BTC/TPPO mediated cascade heterocyclization, which afforded desired products with moderate to high yields. The mechanistic study revealed the reaction underwent a non-isocyanate mechanism, where the component of BTC/TPPO system under different temperature played crucial rules in both steps of cyclization. Besides, the proposed mechanism implicated the TPPDC worked in a catalytic manner in the second heterocyclization, which was shaded by the high concentration requirement of the first heterocyclization. The protocol provided a convenient way to

access the 2,4-dichloro pyrano[2,3-*d*]pyrimidines and furo[2,3-*d*]pyrimidines, where the chlorinated sites could be functionalized easily for further biological investigation.

Experiment Section

General Information Synthetic reagent were purchased from Aladdin, and used without further purification, unless otherwise indicated. **DANGEROUS: BTC WILL RELEASE PHOSGENE IN MOISTURE ENVIRONMENT, ESPECIALLY AT ELEVATED TEMPERATURE. IT'S HIGHLY NOT RECOMMEND TO ADD BTC OVER 80 °C.** Analytical TLC (thin-layer chromatography) was performed with 0.25 mm Silica gel G with a 254 nm fluorescent indicator. Melting points (m.p.) were obtained on a digital melting point apparatus and uncorrected. NMR spectra were recorded with 400 and 600 MHz spectrometer for ^{1}H NMR, 151 and 101 MHz for ^{13}C NMR, and 243 MHz for ^{31}P NMR. TMS was used as internal standard for ^{1}H and ^{13}C NMR, while D_2O and phosphoric acid was used as internal standard for ^{31}P NMR. High resolution mass spectra were measured with HRMS-EI-Q-TOF and HRMS-ESI-Q-TOF. Single-crystal diffraction data for compound **2i** were collected with an Xcalibur, Eos, Gemini Ultra diffractometer. CCDC 1562782 (for **2i**) contain the supplementary crystallographic data for this paper. Purification of products was accomplished by column chromatography (*n*-hexane/ethyl acetate = 10/1) on Silica gel. The substrate 2-(3-oxo-1,3-diarylpropyl)malononitrile and 2-(2-oxo-2-phenylethyl)malononitrile were synthesized according to well established methods.[17]

General Procedure for the synthesis of 2,4-dichloro pyrano[2,3-*d*]pyrimidine. BTC (297 mg, 1 mmol in 5 mL PhCl) was added to a stirred solution of TPPO (834 mg, 3 mmol in 5 mL PhCl) dropwise under ice bath. After complete addition, the mixture was stirred for 30 minutes at room temperature. Then 2-(1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)malononitrile **1a** (309 mg, 1 mmol) was added, and the mixture was heated to 110 °C until completion of reaction (followed by TLC, *n*-hexane/ethyl acetate = 10/1). After cooling down, the mixture was then pour in to the ice water, and extracted with dichloromethane, the organic layer was dried over anhydrous Na_2SO_4, concentrated**.** After the concentration of organic layer extracted during the work-ups, the residue was stirred vigorously in *n*-hexane (20 mL x 3) for 30 mins. Then, the remaining paste was recrystallized using ethanol, which afford TPPO (676 mg, 81% recovery) as a white solid. The *n*-hexane portion was then concentrated and purified over column chromatography (*n*-hexane/ethyl acetate = 10/1) to afford the pure product: ***2,4-dichloro-5-(4-chlorophenyl)-7-phenyl-5H-pyrano[2,3-d]pyrimidine* (2a).** White solid (330 mg, 85% yield), m.p. 137.7-138.4 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70-7.64 (m, 2H), 7.43-7.36 (m, 3H), 7.32 (dt, J = 2.8, 9.2 Hz, 2H), 7.18 (dt, J = 2.4, 8.8 Hz, 2H), 5.78(d,

J = 5.2 Hz, 1H), 4.83 (d, *J* = 5.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.3, 162.4, 158.0, 147.3, 140.3, 133.5, 131.0, 129.6, 129.4, 129.1, 128.5, 124.7, 112.9, 102.3, 38.6; HRMS (EI-Q-TOF) m/z: $[M]^+$ Calcd for $C_{19}H_{11}Cl_3N_2O$ 387.9937; Found 387.9939.

***2,4-dichloro-5,7-diphenyl-5H-pyrano[2,3-d]pyrimidine* (2b).** White solid (292 mg, 82% yield), m.p. 88.4-90.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74-7.63 (m, 2H), 7.44-7.31 (m, 5H), 7.31-7.15 (m, 3H), 5.83 (d, *J* = 5.2 Hz, 1H), 4.85 (d, *J* = 5.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.4, 162.4, 157.8, 147.0, 141.8, 131.2, 129.4, 128.9, 128.4, 128.1, 127.6, 124.6, 113.4, 102.8, 39.2; HRMS (EI-Q-TOF) m/z: $[M]^+$ Calcd for $C_{19}H_{12}Cl_2N_2O$ 354.0327; Found 354.0327.

***2,4-dichloro-5-phenyl-7-p-tolyl-5H-pyrano[2,3-d]pyrimidine* (2c).** White solid (334 mg, 91% yield), m.p. 121.6-123.5 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.38-7.16 (m, 7H), 5.77 (d, *J* = 5.2 Hz, 1H), 4.82 (d, *J* = 5.2 Hz, 1H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, *Chloroform-d*) δ 165.7, 162.7, 158.0, 147.4, 142.3, 139.8, 129.4, 129.1, 128.7, 128.4, 127.8, 124.8, 113.8, 102.2, 39.5, 21.7; HRMS (EI-Q-TOF) m/z: $[M]^+$ Calcd for $C_{20}H_{14}Cl_2N_2O$ 368.0483; Found 368.0486.

***2,4-dichloro-7-(4-methoxyphenyl)-5-phenyl-5H-pyrano[2,3-d]pyrimidine* (2d).** Yellow solid (326 mg, 85% yield), m.p. 153.5-155.1 °C; ^{1}H NMR (400 MHz, *Chloroform-d*) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.37-7.19 (m, 5H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.68 (d, *J* = 4.8 Hz, 2H), 4.82 (d, *J* = 4.8 Hz, 2H), 3.84 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.5, 162.4, 160.5, 147.0, 146.8, 142.2, 128.8, 128.1, 127.5, 126.2, 123.9, 113.9, 113.6, 101.1, 55.4, 39.2; HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{15}Cl_2N_2O_2$ 385.0505; Found 385.0491.

***4-(2,4-dichloro-5-phenyl-5H-pyrano[2,3-d]pyrimidin-7-yl)phenol* (2e).** White solid (294 mg, 75% yield), m.p. 193.3-195.2 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (dt, *J* = 3.2, 9.6 Hz, 2H), 7.37-7.20 (m, 5H), 6.86 (dt, *J* = 3.2, 9.6 Hz, 2H), 5.67 (d, *J* = 4.8 Hz, 1H), 5.56 (br s, 1H), 4.81 (d, *J* = 4.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.5, 162.5, 156.9, 147.1, 142.1, 128.9, 128.1, 127.6, 126.5, 123.9, 116.0, 115.5, 113.6, 101.1, 39.2; HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{12}Cl_2N_2O_2Na$ 393.0168; Found 393.0161.

***2,4-dichloro-7-(4-fluorophenyl)-5-phenyl-5H-pyrano[2,3-d]pyrimidine* (2f).** White solid (293 mg, 79% yield), m.p. 149.8-151.3 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70-7.62 (m, 2H), 7.38-7.32 (m, 2H), 7.31-7.20 (m, 3H), 7.13-7.03 (m, 2H), 5.76 (d, *J* = 5.2 Hz, 1H), 4.83 (d, *J* = 4.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.2, 163.5 (d, $^{1}J_{C\text{-}F}$= 190 Hz), 161.9, 157.8, ,146.2, 141.8, 128.9, 128.0, 127.6, 127.5, 126.7 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz),115.5 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 113.3, 102.7, 39.2; HRMS (EI-Q-TOF) m/z: $[M]^+$ Calcd for $C_{19}H_{11}Cl_2FN_2O$ 372.0232; Found 372.0225.

***7-(3-bromophenyl)-2,4-dichloro-5-phenyl-5H-pyrano[2,3-d]pyrimidine* (2g).** White solid (259 mg, 81% yield), m.p. 149.8-151.3 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (s, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.50

(d, *J* = 8.0 Hz, 1H), 7.39-7.17 (m, 6H), 5.84 (d, *J* = 5.2 Hz, 1H), 4.84 (d, *J* = 4.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.1, 162.6, 157.9, 145.7, 141.5, 133.3, 132.4, 129.9, 129.0, 128.1, 127.7, 123.2, 122.7, 113.2, 104.1, 39.2; HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{12}Cl_2BrN_2O$ 432.9505; Found 432.9499.

***2,4-dichloro-7-(4-chlorophenyl)-5-phenyl-5H-pyrano[2,3-d]pyrimidine* (2h).** White solid (298 mg, 77% yield), m.p. 169.4-173.4 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (dt, *J* = 2.8, 9.2 Hz, 2H), 7.40-7.31 (m, 4H), 7.31-7.21 (m, 3H), 5.81 (d, *J* = 5.2 Hz, 1H), 4.84 (d, *J* = 5.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.2, 162.5, 157.9, 146.1, 141.6, 135.4, 129.8, 128.9, 128.7, 128.0, 127.7, 126.0, 113.3, 103.3, 39.2; HRMS (EI-Q-TOF) m/z: $[M]^+$ Calcd for $C_{19}H_{11}Cl_3N_2O$ 387.9937; Found 387.9939.

***2,4-dichloro-7-phenyl-5-p-tolyl-5H-pyrano[2,3-d]pyrimidine* (2j).** White solid (320 mg, 87% yield), m.p. 121.6-123.5 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74-7.62 (m, 2H), 7.43-7.36 (m, 3H), 7.19-7.10 (m, 4H), 5.81 (d, *J* = 4.8 Hz, 1H), 4.80 (d, *J* = 5.2 Hz, 1H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.3, 162.4, 157.6, 146.8, 138.9, 137.3, 131.2, 129.5, 129.3, 128.4, 128.0, 124.6, 113.6, 103.0, 38.7, 21.2; HRMS (EI-Q-TOF) m/z: $[M]^+$ Calcd for $C_{20}H_{14}Cl_2N_2O$ 368.0483; Found 368.0486. The X-ray analysis data of **2j** is shown in the Supporting Information, Table S1.

***2,4-dichloro-5-(2,4-dichlorophenyl)-7-phenyl-5H-pyrano[2,3-d]pyrimidine* (2k).** White solid (350 mg, 83% yield), m.p. 182.4-185.6 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70-7.62 (m, 2H), 7.48-7.35 (m, 4H), 7.22 (dd, *J* = 4.0, 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 5.75 (d, *J* = 4.8 Hz, 1H), 5.35(d, *J* = 4.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.9, 162.5, 158.5, 147.7, 137.8, 134.0, 133.2, 131.0, 130.6, 129.6, 128.4, 128.1, 124.6, 111.9, 100.2, 35.9; HRMS (EI-Q-TOF) m/z: $[M]^+$ Calcd for $C_{19}H_{10}Cl_4N_2O$ 421.9547; Found 421.9546.

***2,4-dichloro-5-(4-nitrophenyl)-7-phenyl-5H-pyrano[2,3-d]pyrimidine* (2l).** White solid (295 mg, 74% yield). m.p. 153.4-155.2 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.73-7.65 (m, 2H), 7.46-7.39 (m, 5H), 5.78 (d, *J* = 4.8 Hz, 1H), 5.01 (d, *J* = 5.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.3, 162.4, 158.6, 148.6, 148.0, 147.1, 130.7, 129.9, 129.2, 129.0, 124.7, 124.2, 112.1, 101.2, 39.1; HRMS (EI-Q-TOF) m/z: $[M]^+$ Calcd for $C_{19}H_{11}Cl_2N_3O_3$ 399.0177; Found 399.0171.

***2,4-dichloro-5-(4-methoxyphenyl)-7-p-tolyl-5H-pyrano[2,3-d]pyrimidine* (2m).** White solid (374 mg, 94% yield), m.p. 139.8-141.5 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.16 (dt, *J* = 2.8, 9.6 Hz, 2H), 6.86 (d, *J* = 3.2, 10.0 Hz, 2H), 5.75 (d, *J* = 5.2 Hz, 1H), 4.77 (d, *J* = 5.2 Hz, 1H), 3.80 (s, 3H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.3, 162.4, 158.8, 157.6, 147.0, 139.5, 134.3, 129.2, 129.1, 128.6, 124.6, 114.2, 113.8, 102.2, 55.3, 38.3, 21.4; HRMS (EI-Q-TOF) m/z: $[M]^+$ Calcd for $C_{21}H_{16}Cl_2N_2O_2$ 398.0589; Found 398.0594.

***2,4-dichloro-5-(4-chlorophenyl)-7-(4-fluorophenyl)-5H-pyrano[2,3-d]pyrimidine* (2n).** White solid (308 mg, 76% yield), m.p. 146.6-148.2 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73-7.57 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.13-7.03 (m, 2H), 5.71 (d, *J* = 5.2 Hz, 1H), 4.82 (d, *J* = 4.8 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.1, 163.5 (d, $^1J_{C\text{-}F}$ = 199.4 Hz), 162.0, 158.0, 146.5, 140.2, 133.5, 129.4, 129.1, 127.3, 126.7 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 22 Hz), 112.8, 102.1, 38.6; HRMS (EI-Q-TOF) m/z: [M]$^+$ Calcd for $C_{19}H_{10}Cl_3FN_2O$ 405.9843; Found 405.9850.

***2,4-dichloro-5-(2,6-dimethylphenyl)-7-(p-tolyl)-7H-pyrano[2,3-d]pyrimidine* (2o).** White solid (179.1 mg, 45%), m.p. 178.3-179.0 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.13 – 7.07 (m, 2H), 6.95 (m, 1H), 5.51 (d, *J* = 4.8 Hz, 1H), 5.33 (d, *J* = 4.8 Hz, 1H), 2.57 (s, 3H), 2.37 (s, 3H), 2.00 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.5, 161.9, 158.2, 147.7, 139.8, 137.3, 137.2, 136.3, 131.1, 129.4, 128.9, 128.6, 127.8, 124.7, 114.0, 99.2, 34.7, 21.4, 21.4, 20.1; HRMS (ESI-Q-TOF) m/z: [M + H]$^+$ Calcd for $C_{22}H_{19}Cl_2N_2O$ 397.0869; Found 397.0857.

***2,4-dichloro-5-ethyl-7-phenyl-5H-pyrano[2,3-d]pyrimidine* (2p).** Yellow oil (128.8 mg, 42%); ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.73 – 7.69 (m, 2H), 7.46 – 7.39 (m, 3H), 5.76 (d, *J* = 5.4 Hz, 1H), 3.80-3.74 (m, 1H), 1.93 – 1.79 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.8, 161.6, 157.7, 149.3, 131.8, 129.6, 128.8, 124.9, 114.3, 102.0, 33.7, 28.9, 9.7; HRMS (ESI-Q-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{13}Cl_2N_2O$ 307.0399; Found 307.0388.

***2,4-dichloro-5-methyl-7-phenyl-5H-pyrano[2,3-d]pyrimidine* (2q)**. Colorless oil (148 mg, 51% yield); ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.73 – 7.62 (m, 2H), 7.44 – 7.35 (m, 3H), 5.73 (d, *J* = 4.8 Hz, 1H)3.77 (qd, *J* = 6.6, 4.8 Hz, 1H), 1.45 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.1, 161.7, 157.8, 148.2, 131.8, 129.6, 128.7, 124.8, 115.5, 104.0, 27.8, 22.7; HRMS (ESI-Q-TOF) m/z: [M + Na]$^+$ Calcd for $C_{14}H_{10}Cl_2N_2NaO$ 315.0062; Found 315.0071.

***2,4-dichloro-7-phenyl-5H-pyrano[2,3-d]pyrimidine* (2r**). White solid (186 mg 67% yield), 170.5-171.2 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.67 – 7.59 (m, 2H), 7.42 – 7.33 (m, 3H), 5.64 (t, *J* = 2.4 Hz, 1H), 3.52 (d, *J* = 4.2 Hz, 2H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.3, 161.8, 157.9, 149.0, 131.6, 129.5, 128.6, 124.5, 110.4, 97.2, 22.5; HRMS (ESI-Q-TOF) m/z: [M + Na]$^+$ Calcd for $C_{13}H_8Cl_2N_2NaO$ 300.9906; Found 300.9897.

***2,4-dichloro-5-(furan-2-yl)-7-phenyl-5H-pyrano[2,3-d]pyrimidine* (2s).** White solid (262 mg, 76% yield), m.p. 85.6-87.6 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76-7.66 (m, 2H), 7.43-7.37 (m, 3H), 7.33 (dd, *J* = 0.8, 2.0 Hz, 1H), 6.34 (dd, *J* = 1.6, 3.2 Hz, 1H), 6.18 (d, *J* = 3.2 Hz, 1H), 5.83 (d, *J* = 4.8 Hz, 1H), 5.02 (d, *J* =5.2 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.4, 162.3, 157.9, 152.7, 148.5, 142.4, 131.1, 129.5, 128.4, 124.7, 111.0, 110.5, 107.2, 99.4, 32.6; HRMS (EI-Q-TOF) m/z: [M]$^+$ Calcd for $C_{17}H_{10}Cl_2N_2O_2$ 344.0119; Found 344.0123.

***2,4-dichloro-7-phenyl-5-(thien-2-yl)-5H-pyrano[2,3-d]pyrimidine* (2t).** White solid (264 mg, 73% yield), m.p. 85.6-87.6 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75-7.64 (m, 2H), 7.44-7.38 (m, 3H), 7.24 (dd, *J* = 1.6, 5.2 Hz, 1H), 7.00-6.94 (m, 2H), 5.92 (d, *J* = 5.2 Hz, 1H), 5.19 (d, *J* = 5.2 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 164.9, 162.3, 157.8, 147.8, 145.2, 131.2, 129.6, 128.5, 126.9, 125.7, 125.4, 124.8, 113.2, 102.2, 33.8; HRMS (EI-Q-TOF) m/z: [M]$^+$ Calcd for $C_{17}H_{10}Cl_2N_2OS$ 359.9891; Found 359.9885.

***(E)-2,4-dichloro-7-styryl-5-(p-tolyl)-5H-pyrano[2,3-d]pyrimidine* (2w).** White solid (311.7 mg, 79%), m.p. 158.0-158.4 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.63 – 7.60 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.31 – 7.25 (m, 4H), 7.23 (d, *J* = 7.8 Hz, 2H), 6.56 (d, *J* = 15.6 Hz, 1H), 6.20 (dd, *J* = 16.2, 7.8 Hz, 1H), 5.70 (d, *J* = 5.4 Hz, 1H), 4.46 (dd, *J* = 7.8, 5.4 Hz, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.8, 162.5, 158.1, 148.8, 140.0, 136.2, 132.8, 129.5, 128.8, 128.8, 128.3, 127.8, 126.6, 124.8, 113.0, 99.9, 36.1, 21.5; HRMS (ESI-Q-TOF) m/z: [M + H]$^+$ Calcd for $C_{22}H_{17}Cl_2N_2O$ 395.0712; Found 395.0720.

***(E)-2,4-dichloro-9-(4-methylbenzylidene)-5-(p-tolyl)-6,7,8,9-tetrahydro-5H-chromeno[2,3-d]pyrimidine* (2x).** White solid (254.9 mg, 57%), m.p. 168.9-169.3 °C; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.23 (d, *J* = 8.4 Hz, 2H), 7.19 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.12 (s, 4H), 4.45 (s, 1H), 2.79 – 2.73 (m, 1H), 2.63 – 2.56 (m, 1H), 2.36 (s, 3H), 2.32 (s, 3H), 1.73 – 1.58 (m, 4H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.3, 162.1, 157.7, 142.5, 138.3, 137.7, 136.9, 134.1, 129.7, 129.5, 129.1, 128.6, 128.0, 124.4, 116.1, 114.3, 43.8, 27.5, 27.1, 22.3, 21.4, 21.2; HRMS (ESI-Q-TOF) m/z: [M + H]$^+$ Calcd for $C_{26}H_{23}Cl_2N_2O$ 449.1182; Found 449.1174.

General Procedure for the synthesis of 2,4-dichloro furo[2,3-d]pyrimidine. BTC (385 mg, 1.3 mmol in 5 mL PhCl) was added to a stirred solution of TPPO (1112 mg, 4 mmol in 5 mL PhCl) dropwise under ice bath. After complete addition, the mixture was stirred for 30 minutes at room temperature. Then 2-(2-oxo-2-phenylethyl)malononitrile **3a** (184 mg, 1 mmol) was added, and the mixture was heated to 110 °C until completion of reaction (followed by TLC, *n*-hexane/ethyl acetate = 10/1). After cooling down, the mixture was then pour in to the ice water, and extracted with dichloromethane, the organic layer was dried over anhydrous Na_2SO_4, concentrated**.** After the concentration of organic layer extracted during the work-ups, the residue was stirred vigorously in *n*-hexane (20 mL x 3) for 30 mins. Then, the remaining paste was recrystallized using ethanol, which afford TPPO (676 mg, 81% recovery) as a white solid. The *n*-hexane portion was then concentrated and purified over column chromatography (*n*-hexane/ethyl acetate = 10/1) to afford the pure product: After cooling down, the mixture was then pour in to the ice water, and extracted with dichloromethane, the organic layer was dried over anhydrous Na_2SO_4, concentrated and purified over column chromatography (*n*-hexane/ethyl acetate = 10/1) to afford the pure product: ***2,4-dichloro-6-phenylfuro[2,3-d]pyrimidine* (4a)**. White solid (213 mg, 81% yield), m.p. 173.2-174.7 °C; ^{1}H NMR (400 MHz, Chloroform-

d) δ 7.86 (dd, *J* = 1.7, 7.8 Hz, 2H), 7.65-7.42 (m, 3H), 7.05 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 166.8, 157.3, 153.6, 152.5, 130.6, 129.1, 127.5, 125.4, 118.4, 97.4; HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_6Cl_2N_2NaO$ 286.9749; Found 286.9743.

***2,4-dichloro-6-(p-tolyl)furo[2,3-d]pyrimidine* (4b)**. White solid (216 mg, 78%), m.p. 169.5-170.6 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2), 6.97 (s, 1H), 2.43 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 166.8, 157.6, 153.2, 152.2, 141.1, 129.8, 125.4, 124.7, 118.5, 96.5, 21.6; HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_9Cl_2N_2O$ 279.0086; Found 279.0099.

***2,4-dichloro-6-(4-methoxyphenyl)furo[2,3-d]pyrimidine* (4c)**. White solid (250 mg, 85% yield), m.p. 183.6-184.7 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.9 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 6.89 (s, 1H), 3.89 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 166.3, 161.0, 157.0, 126.8, 119.9, 118.5, 114.4, 95.3, 55.6; HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_9Cl_2N_2O_2$ 295.0036; Found 295.0025.

***2,4-dichloro-6-(4-chlorophenyl)furo[2,3-d]pyrimidine* (4d).** Yellow solid (208 mg, 70% yield), m.p. 209.1-210.6 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 7.1 Hz, 2H), 7.05 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 166.3, 155.6, 153.4, 152.3, 136.4, 129.1, 126.4, 125.8, 118.0, 97.7; HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_6Cl_3N_2O$ 298.9540; Found 298.9532.

***2,4-dichloro-6-(4-fluorophenyl)furo[2,3-d]pyrimidine* (4e).** Orange solid (351 mg, 87%); m.p. 196.9-198.2 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (dd, *J* = 5.2, 8.7 Hz, 2H), 7.20 (t, *J* = 8.5 Hz, 2H), 7.00 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 166.2, 163.3 (d, $^{1}J_{C\text{-}F}$ = 250.5 Hz), 155.8, 153.2, 152.1, 127.3 (d, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 123.6, 118.1, 116.2 (d, $^{2}J_{C\text{-}F}$ = 22.0 Hz) , 97.0; HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_6Cl_2FN_2O$ 282.9836; Found 282.9822.

***2,4-dichloro-5,6-diphenylfuro[2,3-d]pyrimidine* (4f).** White solid (285 mg, 84% yield), m.p. 121.7-123.9 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58-7.40 (m, 7H), 7.39-7.27 (m, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 165.5, 153.2, 152.6, 151.7, 131.8, 130.1, 129.6, 129.2, 128.5, 128.5, 128.3, 127.5, 126.8, 117.4, 114.7; HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{10}Cl_2N_2NaO$ 363.0062; Found 363.0086.

***2,4-dichloro-6-(4-methoxyphenyl)-5-phenylfuro[2,3-d]pyrimidine* (4g).** White solid (318 mg, 86% yield), m.p. 147.2-148.1 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54-7.38 (m, 7H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 166.0, 160.8, 153.1, 152.4, 152.4, 130.6, 129.8, 128.8, 120.4, 118.0, 114.2, 113.1, 55.4; HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{12}Cl_2N_2NaO_2$ 393.0168; Found 393.0163.

***2,4-dichloro-5-(2-chlorophenyl)-6-(4-methoxyphenyl)furo[2,3-d]pyrimidine* (4h)**. White solid (311 mg, 77% yield), m.p. 148.2-149.7 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 8.0 Hz, 1H) 7.52-7.43 (m, 3H), 7.39 (d, *J* = 4.8 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 3.82 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-

d) δ 166.1, 161.0, 153.3, 152.8, 152.4, 135.4, 132.2, 130.5, 129.9, 129.3, 128.4, 127.2, 120.3, 117.9, 114.4, 110.1, 55.4; HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{11}Cl_3N_2NaO_2$ 426.9778; Found 426.9783.

***2,4-dichloro-5-(2-fluorophenyl)-6-(4-methoxyphenyl)furo[2,3-d]pyrimidine* (4i).** White solid (314 mg, 81% yield), m.p. 161.1-162.2 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 - 7.47 (m, 3H), 7.39 (td, *J* = 7.5, 1.9 Hz, 1H), 7.30-7.21 (m, 2H), 6.85 (dt, *J* = 8.0, 2.2 Hz, 2H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR 165.6, 161.3, 160.5, 158.8, 152.7, 151.9, 132.0, 130.9, 130.8, 128.2, 124.2, 120.0, 117.7, 117.5, 116.0, 115.7, 114.1, 106.3, 55.6; HRMS(ESI-Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{12}Cl_2FN_2O_2$ 389.0254; Found 389.0266.

***2,4-dichloro-6-phenylthieno[2,3-d]pyrimidine* (5a).** Brown oil (163 mg, 58% yield); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73-7.65 (m, 2H), 7.53 (s, 1H), 7.51-7.41 (m, 3H); ^{13}C{H} NMR (101 MHz, Chloroform-d) δ ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 169.0, 154.2, 153.3, 146.3, 131.8, 129.8, 129.5, 129.1, 126.5, 113.7; HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_7Cl_2N_2S$ 280.9702; Found 280.9688.

General Procedure for the *In-situ* ^{31}P NMR test. The reaction was conducted in a standard 5 mm NMR tube with D_2O and phosphonic acid in an internal standard capillary. The signal was collected at 25 °C. The reaction was performed under 0.05 mmol scale and heated outside the apparatus, which was sent to test at the time designated on the spectrums. After the NMR test, the yield of **2a** was about 40%.

Associate Content

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

^{31}P NMR study of low-temperature species, single crystal X-ray diffraction data for compound **2j**, ^{1}H and ^{13}C NMR spectrum for all compounds (PDF)

X-ray crystallographic data for compound **2j** (CIF)

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Notes

The authors declare no competing financial interest.

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