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FACILE AND EFFICIENT CYCLIZATION OF ANTHRANILONITRILE TO 2,4-DICHLOROQUINAZOLINE BY BIS(TRICHLOROMETHYL) CARBONATE AND CATALYTIC AMOUNT TRIPHENYLPHOSPHINE OXIDE

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Abstract – 2,4-Dichloroquinazolines were synthesized by the cyclization of anthranilonitrile using *bis*(trichloromethyl) carbonate (BTC) with the aid of catalytic amount of triphenylphosphine oxide (Ph_3PO) at 120 °C. This method was also applied to the synthesis of 2,4-dichlorothieno[2,3-d]pyrimidine. The plausible mechanism is presented.

INTRODUCTION

Quinazoline derivatives have been shown to be promising pharmaceutical agents for the treatment of viral diseases[1] and cancer.[2,3] In addition, quinazoline derivatives often served as precursors to 2,4-dichloroquinazolines, which were widely used as intermediates in the synthesis of a variety of pharmaceutical agents.[3,4] Important drugs of the quinazoline family in current use for the treatment of hypertension are prozocin,[5] doxazosin,[6] and so on (Figure 1).

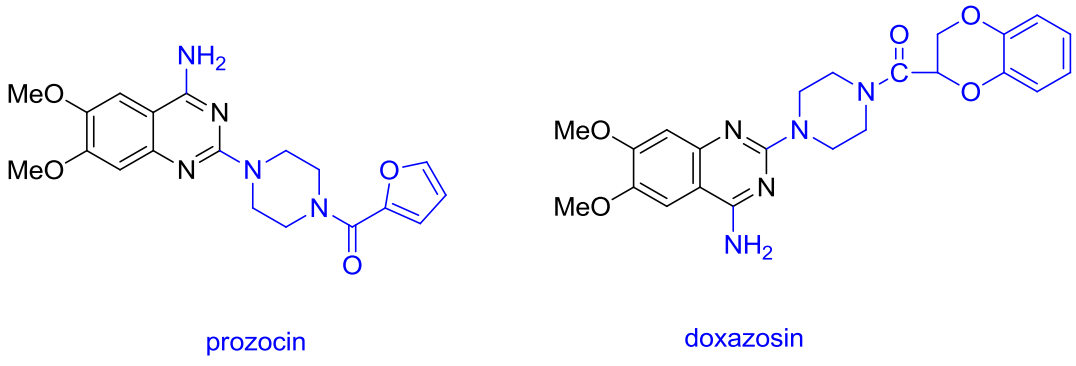


Figure 1

The combination of pharmacological application and synthetic utility has generated interest in the development of methodology for the synthesis of quinazoline derivatives. 2,4-Dichloroquinazolines have been prepared in a conventional manner from the corresponding 2,4-dihydroxyquinazolines, which was prepared by antranylic acid,[7] 2-aminobenzoate[8,9] or anthranilonitrile,[10] etc, followed by chlorination using excess phosphoryl chloride.[7-11] However, according to our knowledge, there have been few reports of the direct synthesis of 2,4-dichloroquinazolines from aniline analogues until now. The first example reported by Chi *et al.* described one-step cyclization of anthranilonitrile to 2,4-dichloroquinazoline using diphosgene and acetonitrile system.[12] However, this method suffered from several drawbacks such as use of toxic diphosgene, harsh reaction conditions and relatively low yields.

Based on the postulated mechanism of this protocol and our previous studies on dichlorotriphenyl phosphine (PPh_3Cl_2),[13,14] which can be generated *in situ* by *bis*(trichloromethyl) carbonate (BTC, triphosgene) and triphenylphosphine oxide (Ph_3PO), we examined their reactivity the novel system combined by BTC and Ph_3PO toward this reaction. As a result, we achieved facile and efficient one-pot synthesis of 2,4-dichloroquinazolines by the cyclization of anthranilonitrile using BTC with the aid of catalytic amount of Ph_3PO. Herein, we wish to report our preliminary results in this area.

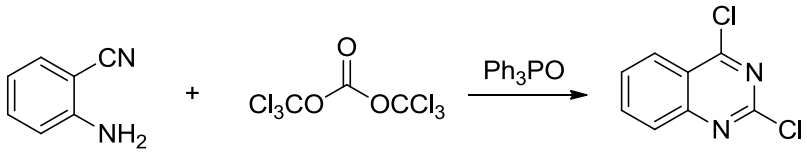
RESULTS AND DISCUSSION

Initially, we started our investigation using anthranilonitrile **1a** as the model substrate to examine its behavior under different conditions. Upon treatment of **1a** with 2.0 equiv BTC and 1.0 equiv Ph_3PO at 100 ^oC for 3.0 h, the reaction proceeded smoothly as indicated by TLC and furnished one product with 85 % yield after workup and purification by column chromatography. From the spectral and analytical data, the product was characterized as 2,4-dichloroquinazoline **2a** (Scheme 1).

Subsequently, the reaction conditions, including reaction temperature, solvent and the ration of **1a** to BTC and Ph_3PO, were then investigated. It was found that the reaction temperature at around 120 °C was effective for the reaction of **1a** to form product **2a** with the yield of 95%. Besides chlorobenzene, other solvents such as toulene, *o*-xylene and 1,1,2,2-tetrachloroethane were compared, but the conversion was relatively low. Moreover, experimental result revealed that the yield was not affected with a higher molar ratio of Ph_3PO to **1a** (Table 1, entry 2) or BTC to **1a** (Table 1, entry 3).

Stimulated by our previous finding that dichlorotriphenylphosphine (PPh_3Cl_2) can be formed from Ph_3PO and BTC,[14] we reasoned that a reaction cycle could be established between Ph_3PO and PPh_3Cl_2 in the above reaction. To our delight, when the protocol was applied, **2a** were successfully obtained with 2.1 equiv BTC and a catalytic amount of Ph_3PO (0.2 equiv) to give excellent yield of 2,4-dichloroquinazoline by prolonging the reaction time to 6 h (Table 1, entry 7), indicating that the reaction cycle could proceed smoothly. However, the yield was reduced significantly with 0.1 equiv. Ph_3PO (Table 1, entry 8).

Table 1. Synthesis of **2a** from **1a** with different amount of Ph_3PO and BTC[a]



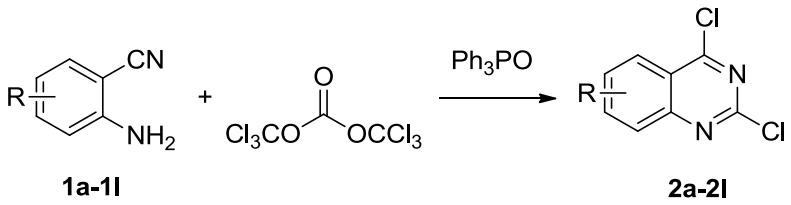
1a **2a**

Entry	Ratio : Ph_3PO /BTC /**1a** (equiv)	Temp. (^oC)	Time (h)	Yield of **2a**[b] (%)
1	1 : 2 : 1	100	3	85.0
2	1 : 2 : 1	120	1	95.0
3	1.5 : 2 : 1	120	1	95.5
4	1 : 3 : 1	120	1	94.0
5	0.5 : 2 : 1	120	4	93.0
6	0.2 : 2 : 1	120	6	92.0
7	0.2 : 2.1 : 1	120	6	95.0
8	0.1 : 2 : 1	120	6	78.0

[a]Reaction conditions: BTC was dropped into Ph_3PO at -5~0 °C , followed by stirring at room temperature for 30 min, then **1a** was added and the temperature was rise to 120 °C.
[b] Isolated yields based on **1a**

Having established the optimal conditions for the cyclization, We next turned our attention to exploring the scope and generality of this method for the synthesis of other 2,4-dichloroquinazolines. A wide range of substituted and structurally diverse anthranilonitriles **1** prepared by the reaction of appropriate substituted isatin[15] were subjected to this reaction under similar conditions. The results were summarized in Table 2. Gratifyingly, under the optimized conditions, all the substrates listed in Table 2 afforded the desired products **2** in good to excellent yields. Table 2 indicated the following trends that compounds **1** with electron-donating groups produced the 2,4-dichloroquinazolines **2** in excellent yields (Table 2, entries 2–5), while with electron-withdrawing groups afforded the products in relatively lower yields (Table 3, entries 6–12). At this stage, it could be concluded that our protocol tolerates a wide variety of anthranilonitriles.

Table 2. Synthesis of **2** form **1** by Ph_3PO and BTC system



1a-1l **2a-2l**

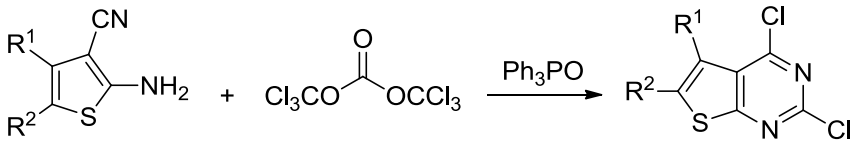
Entry	Product	R (2a-2l)	Time (h)	Yield[a] (%)
1	**2a**	H	6	95.0
2	**2b**	6-OMe	6	96.0
3	**2c**	6-Me	6	95.1
4	**2d**	6,7-diOMe	8	94.8
5	**2e**	5,7-diMe	8	93.5
6	**2f**	6-Cl	8	90.3
7	**2g**	8-Cl	8	89.6
8	**2h**	7-F	6	88.0
9	**2i**	6-F	10	88.8
10	**2j**	6-Br	10	93.2
11	**2k**	6-NO_2	10	80.0
12	**2l**	5,7-diCl	10	75.4

[a]Reaction conditions: BTC (2.1 mmol) was dropped into Ph_3PO (0.6 mmol) at -5~0 °C, followed by stirring at room temperature for 30 min, then **1** (3 mmol) was added and the temperature was rise to 120 °C.

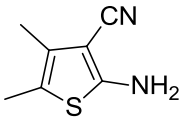
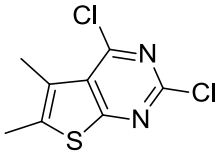
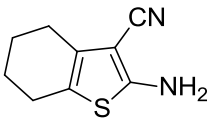
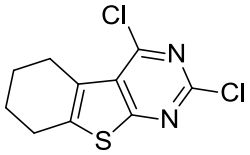
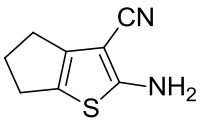
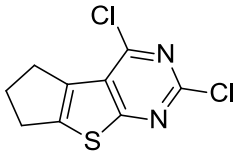
[b] Isolated yields based on **1**.

To further extend the scope and generality of this reaction, another example was attempted to show that this reaction is generally applicable to the synthesis of other pyrimidine-containing heterocyclic compounds. Substitued aminothiophene nitriles **3**, which were prepared by the reaction of appropriate ketones, propanedinitriles, and elemental sulfur in the presence of Et_2NH at 120 °C,[16] reacted with BTC and Ph_3PO under the similar conditions to afford 2,4-dichlorothieno[2,3-*d*]pyrimidines **4**. The results showed that this reaction is a very reliable method for the synthesis of thienopyrimidines **4** with moderate to good yields.

Table 3. Synthesis of **4** from **3** by Ph_3PO and BTC system



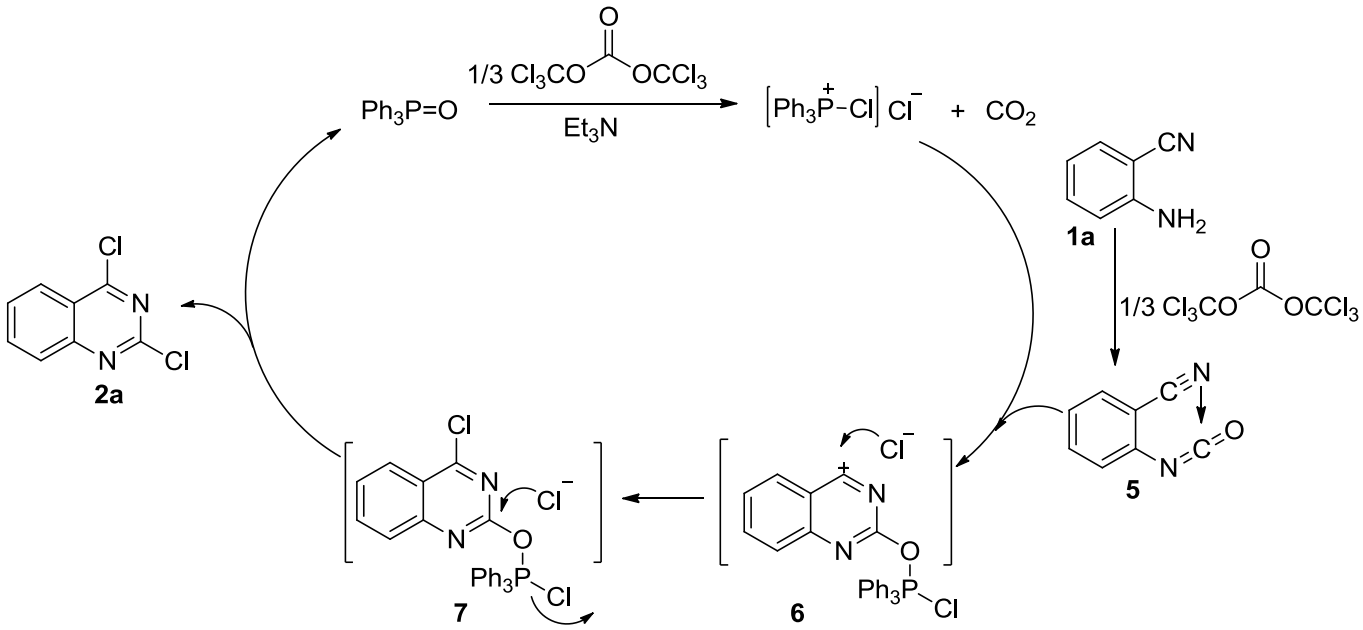
3a-3c **4a-4c**

Entry	Reactants	Products	Time (h)	Yield (%)
1	 **3a**	 **4a**	7	77.0
2	 **3b**	 **4b**	6	90.1
3	 **3c**	 **4c**	7	83.5

[a]Reaction conditions: BTC (2.1 mmol) was dropped into Ph_3PO (0.6 mmol) at -5~0 °C, followed by sirring at room temperature for 30 min, then **3** (3 mmol) was added and the temperature was rise to 120 °C.

[b]Isolated yields based on **3**.

On the basis of the above results and previous literatures,[12,13] a reaction mechanism for the formation of 2,4-dichloroquinazolines from athranilonitrile is presented in Scheme 1. Athranilonitrile **1a** first reacts with BTC to afford compound **5**. Further reaction of **5** with Ph_3PCl_2 generated *in situ* from BTC and Ph_3PO, forms the O-P bond and gets the intermediate **6**. Finally primary chlorination of the C4 position, secondary chlorination of the C2 position is performed by the replacement of Ph_3PO leaving group with chloride, to yield the corresponding 2,4-dichloroquinazoline **2a**.



Scheme 1

In summary, we have successfully developed a new method for the synthesis of 2,4-dichloroquinazolines by using BTC and Ph_3PO. The mild cycle reaction condition, convenient operational procedure, and good yield were the notable advantages. Moreover, 2,4-dichlorothieno[2,3-*d*]pyrimidine can be synthesized from aminothiophene nitrile. It could therefore be concluded that our synthetic method has significant generality for the synthesis of many pyrimidine-containing heterocyclic compounds. We believe this strategy will bring a more practical alternative to the existing methods in the future.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. Melting points (mp) were obtained on digital melting point apparatus WRS-1B and are uncorrected. ^{1}H NMR, ^{13}C NMR were recorded at VARAIN-400 on a 400 MHz and 100 MHz, respectively, and TMS as internal standard. IR spectra (KBr) were recorded on AVATAR-370. All reactions were monitored by TLC with GF254 silica gel coated plates. Column chromatography was carried out on silica gel.

General procedure for the synthesis of 2,4-dichloroquinazolines (2a~2l)

To an ice-cold magnetically stirred solution of PhCl (5 mL) and Ph_3PO (0.17 g, 0.6 mmol), added four drops of Et_3N, *bis*(trichlormethyl)carbonate (0.63 g, 2.1 mmol/6 mL PhCl) was added dropwise. The reaction mixture was placed to room temperature for 30 min. Then athranilonitriles **1a~1l** (3 mmol) was

added, rise the temperature to 120 °C for 6 h. When the reaction was completed, poured the mixture into water and extracted with EtOAc. After dryness and condensation, the crude reaction product was separated by column chromatography using 10% EtOAc in petroleum ether as eluent to afford pure **2a~2l**.

2,4-Dichloroquinazolines (2a).

White solid, mp 119.3–121.0 °C (lit.,[3] 118 °C). ^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.26 (d, J = 8.4 Hz, 1H), 8.01–7.97 (m, 2H), 7.76 – 7.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 163.7, 154.9, 152.1, 135.9, 129.0, 127.8, 125.8, 122.2.

2,4-Dichloro-6-methoxyquinazoline (2b).

White solid, mp 170–171 °C (lit.,[17] 171 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.89 (d, J = 9.2 Hz, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.40 (d, J = 2.8 Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 161.5, 159.4, 152.5, 148.4, 129.3, 129.0, 123.3, 102.9, 56.0.

2,4-Dichloro-6-methylquinazoline (2c).

White solid, mp 140–141 °C (lit.,[18] 140–141 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.00 (s, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.80 (dd, J = 8.6, 1.8 Hz, 1H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 162.9, 154.0, 150.8, 139.8, 138.2, 127.5, 124.5, 122.2, 22.0.

2,4-Dichloro-6,7-dimethoxyquinazoline (2d).

White soli, mp 160.8–161.7 °C (lit.,[8] 157–159°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.33 (s, 1H), 7.25 (s, 1H), 4.07 (s, 3H), 4.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 159.9, 157.6, 153.4, 151.4, 150.4, 117.7, 106.21, 102.7, 56.8, 56.5. IR (KBr): ν_{max} = 1611, 1546, 1505, 1401, 1238, 1205, 1142, 848 cm^{-1}. MS (ESI): =259.1 ([M+H]$^+$).

2,4-Dichloro-5,7-dimethylquinazoline (2e).

White solid, mp 140.2–143.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.59 (s, 1H), 7.30 (s, 1H), 2.96 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 162.2, 154.6, 154.0, 146.5, 136.2, 134.2, 125.7, 120.0, 24.8, 21.9. HRMS(ESI) $C_{10}H_9Cl_2N_2$ ([M+H]$^+$): calcd. 227.0143, found 227.0148.

2,4,6-Trichloroquinazoline (2f).

White solid, mp 132.5–135.8 °C (lit.,[22] 129.1–130.8 °C). 1H NMR (400 MHz, $CDCl_3$) δ_H: 8.22 (d, J = 2.0 Hz, 1H), 7.98–7.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 162.6, 155.2, 150.6, 136.9, 135.07, 129.5, 124.7, 122.8.

2,4,8-Trichloroquinazoline (2g).

White solid. mp 150.8–152.9 °C (lit.,[19] no data). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.19 (dd, J = 8.8, 1.2 Hz, 1H), 8.07 (dd, J = 7.6, 1.2 Hz, 1H), 7.65 (dd, J = 8.2, 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 164.2, 155.8, 148.9, 135.7, 132.6, 128.8, 124.7, 123.4.

2,4-Dichloro-7-fluoroquinazoline (2h).

White solid, mp 142.3–145.1°C (lit.,[20] no data). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.34–8.24 (m, 1H), 7.62

(d, J = 8.8 Hz, 1H), 7.54–7.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 161.5 (d, J^1 = 295 Hz), 158.1 (s), 150.9 (s), 148.7 (d, J^3 = 14 Hz), 123.8(d, J^3= 11 Hz), 114.5 (s), 114.2 (d, J^3=16 Hz), 106.9 (d, J^2 = 28 Hz).

2,4-Dichloro-6-fluoroquinazoline (2i).

White solid, mp 135.7–137.2 °C (lit.,[22] no data). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.03 (dd, J = 9.2, 4.8 Hz, 1H), 7.87 (dd, J = 8.0, 2.8 Hz, 1H), 7.79–7.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 163.0 (d, J^4 = 6 Hz), 161.1 (d, J^1 = 252 Hz), 154.5 (d, J^4 = 3 Hz), 149.2 (s), 130.7 (d, J^4 = 9 Hz), 126.4 (d, J^2 = 26 Hz), 123.1 (d, J^3 = 10 Hz), 109.7 (d, J^2 = 24 Hz).

6-Bromo-2,4-dichloroquinazoline (2j).

White solid, mp 131.0–136.1 °C (lit.,[23] no data). ^{1}H NMR (400MHz, $CDCl_3$) δ_H: 8.40 (d, J = 2.0Hz, 1H), 8.04 (dd, J = 8.8, 2.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 162.5, 155.2, 150.8, 139.5, 129.5, 128.4, 123.2, 123.1.

2,4-Dichloro-6-nitroquinazoline (2k).

White solid, mp 121.1–123.4 °C (lit.,[7] 122–124 °C). ^{1}H NMR (400 MHz, CDCl3) δ_H: 9.16 (d, J =2.4, Hz, 1H), 8.73 (dd, J = 9.2, 2.4Hz, 1H), 8.16 (dd, J = 9.2, 0.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 162.3, 155.1, 150.6, 139.3, 129.3, 127.9, 123.0, 122.9.

2,4,5,7-Tetrachloroquinazoline (2l).

White solid. mp 100.3–101.2 °C (lit.,[4b] no data). ^{1}H NMR (400MHz, $CDCl_3$) δ_H: 7.90 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 162.0, 156.0, 154.5, 141.3, 132.5, 126.8, 118.8.

2,4-Dichloro-5,6-dimethylthieno[2,3-*d*]pyrimidine (4a).

White solid. mp 150.6–153.7 °C (lit.,[21] no data). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.51 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 169.4, 153.7, 152.4, 136.5, 127.7, 124.7, 14.2, 14.1.

2,4-Dichloro-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidine (4b).

Pale yellow solid, mp 169.8–174.6 °C (lit.,[21] 178–180 °C). 1H NMR (400 MHz, $CDCl_3$) δ_H: 3.07 (t, J = 4.2 Hz, 1H), 2.86 (t, J = 4.2 Hz, 1H), 1.92 (dt, J = 6.1, 2.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 170.2, 153.6, 152.6, 139.9, 127.3, 126.9, 26.2, 26.1, 22.4, 22.2.

2,4-Dichloro-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidine (4c).

Pale yellow solid. mp 129.8–133.5 °C (lit.,[21] 134–135 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.21–3.10 (m, 2H), 3.06 (dd, J = 10.4, 4.2 Hz, 2H), 2.62 – 2.46 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.7, 153.3, 152.3, 145.0, 135.8, 124.6, 30.3, 29.3, 27.4.

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