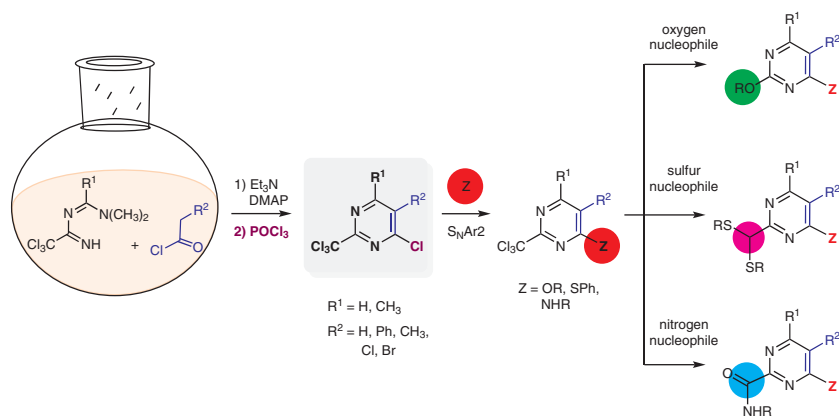


A Synthesis of 4-Chloro-2-(trichloromethyl)pyrimidines and Their Study in Nucleophilic Substitution

Michelle L. Trujillo-Lagunas^aIgnacio Medina-Mercado^aIvann Zaragoza-Galicia^aHoracio F. Olivo^bMoisés Romero-Ortega^{*a}

^a Departamento de Química Orgánica, Facultad de Química, Universidad Autónoma del Estado de México, Toluca, C.P. 50180, México
mromero@uaemex.mx

^b Medicinal and Natural Products Chemistry, The University of Iowa, Iowa City, IA 52242, USA



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Abstract A convenient two-step, one-pot synthesis of 4-chloro-2-(trichloromethyl)pyrimidines starting from 2-(trichloromethyl)-1,3-diazabutadienes is described. These nitrogen heterocycles were prepared by a sequential acylation/intramolecular cyclization reaction between 2-(trichloromethyl)-1,3-diazabutadienes and acyl chlorides in the presence of triethylamine followed by treatment with POCl_3 . This is the first report for the synthesis of this type of 4-chloro-2-(trichloromethyl)pyrimidine derivatives and serves as a source for a wide variety of other substituted pyrimidines by nucleophilic substitution reactions.

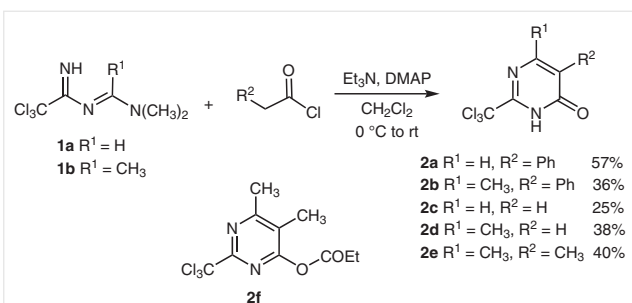
Key words cycloaddition reaction, tetrachloropyrimidines, 1,3-diazabutadienes, intramolecular cyclization, nucleophilic substitution

3,5-Dichloro-4,6-dimethoxy-2-(trichloromethyl)pyridine (Penclomedine)^{1,2} and 2-(trichloromethyl)pyrimidine derivatives have attracted attention because they have remarkable antitumor properties especially against human MX-1 mammary carcinoma.^{3–5} Several structural variants have been designed and synthesized in an attempt to discover related ring structures with nitrogen, oxygen, and sulfur analogues that might exhibit better antitumor activity. A common problem in the synthesis of these chlorinated heterocycles is how to carry out efficient preparations.^{6,7} In this context, cycloaddition reactions employing azadienes in hetero Diels–Alder methodology represents a straightforward and efficient approach for the construction of a wide variety of four-, five-, and six-membered nitrogen-containing heterocycles.^{8–11} Dienes containing two nitrogen atoms have attracted attention in heterocyclic chemistry in recent years because of their importance in the construction of pyrimidines derivatives.^{9,12} A variety of 1,3-diazadienes as 4π components in cycloaddition reactions have been reported,

such as [4+1] cycloaddition process with isocyanides,¹³ the Simmons–Smith reagent,¹⁴ [4+2] with acetylenic esters,^{15,16} enamines,¹⁷ oxazolinones,¹⁸ sulfenes,¹⁹ nitriles,²⁰ and recently with benzyne intermediates.²¹ Particular interest has been given to the cycloaddition reactions of 1,3-diazabutadienes with ketenes; they are reported to undergo [4+2]^{22–25} as well [2+2]^{26–30} cycloaddition reactions leading to several different pyrimidinones and azetidinones. Ketenes are highly electrophilic intermediates, readily generated in solution by reaction of acyl chlorides with non-nucleophilic bases, such as a tertiary amine.³¹ Additionally, ketenes are generally referred to as poor nucleophiles.³² In 1996, Krasodomska and Bogdanowicz-Szwed reported the reaction of 1,3-diazabutadienes with various ketenes, including chloroketenes, for the formation of thiadiazolopyrimidines.³³ Although numerous examples of [4+2] cycloaddition reactions of 1,3-diazabutadiene analogues with ketenes have been published, the majority are of little value with regard to the generation of aromatic heterocyclic compounds.^{22–25} In these examples, 1,3-diazabutadienes bear an alkyl or aryl substituent on N-1, which makes the aromatization of the cycloadduct not possible. We have previously demonstrated the synthetic utility of 1,3-diazabutadienes bearing a hydrogen on N-1 in cycloaddition reactions for the preparation of various aromatic heterocyclic compounds.^{16,21,34,35} In connection with our studies directed at the development of new synthetic methods to prepare 2-(trichloromethyl)pyrimidine derivatives and their potential application in medicinal chemistry, we have been interested in studying the reactivity of these 1-unsubstituted 2-(trichloromethyl)-1,3-diazabutadienes, since these kinds of compounds can undergo cycloaddition reactions with ketenes to produce 2-(trichloromethyl)pyrimidin-4-ones, potential valuable intermediates to build 2-(trichlorometh-

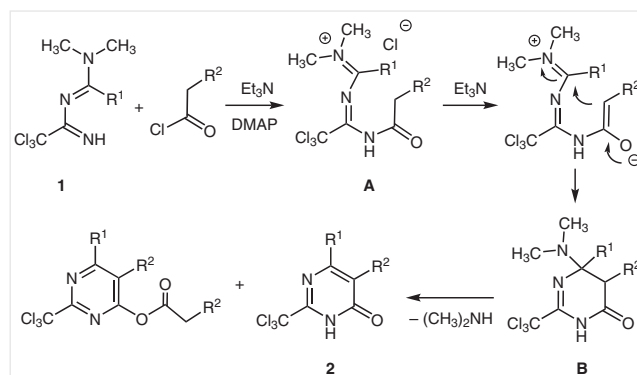
yl)pyrimidine derivatives. Herein we describe our studies on the reactivity of *NH*-1,3-diazadienes with a variety of enolizable acyl chlorides and some reactions of the tetra-chloropyrimidine derivatives thus obtained.

2-(Trichloromethyl)-1,3-diazabuta-1,3-diene **1a** and 2-(trichloromethyl)-1,3-diazapenta-1,3-diene **1b** were prepared from trichloroacetamide and the amide dimethyl acetal (commercially available) in 90–100% yields according to our published procedure.¹⁶ Initially, we believed that enolizable acyl chlorides would react under basic conditions to form ketenes in situ, which in the presence of 2-(trichloromethyl)-1,3-diazadienes **1** would produce 2-(trichloromethyl)pyrimidin-4-one derivatives **2** involving a [4+2] cycloaddition process. Therefore, we commenced our study by using 1,3-diazabutadiene **1a** as a model to evaluate this cycloaddition reaction with phenylacetyl chloride (1.2 equiv) under basic conditions (Et_3N , 1.2 equiv) at 0 °C in CH_2Cl_2 solution. Unfortunately, TLC analysis showed a complex mixture containing only a trace of the 2-(trichloromethyl)pyrimidin-4-one **2a**. A range of experimental approaches were investigated, including solvent screening as well as careful control of the reaction conditions. The best reaction conditions for the formation of **2a** were using 2.2 equivalents of phenylacetyl chloride and 2.2 equivalents of Et_3N in the presence of a catalytic amount of DMAP (10 mol%) from –10 °C to room temperature in CH_2Cl_2 solution. Under these conditions, the desired 2-(trichloromethyl)pyrimidin-4-one **2a** was obtained in 57% yield after silica gel column chromatography purification (Scheme 1). However, when this procedure was applied to 2-(trichloromethyl)-1,3-diazapenta-1,3-diene **1b** the 2-(trichloromethyl)pyrimidin-4-one **2b** was obtained in only 36% yield. The use of this cycloaddition process utilizing acetyl chloride as the acylating agent with both 2-(trichloromethyl)-1,3-diazadienes **1a** and **1b**, was much less successful. Usually, a complex mixture of products containing the 2-(trichloromethyl)pyrimidin-4-one **2c** or **2d** was obtained in 25% and 38% yields, respectively. We found that when propanoyl chloride was used, the 2-(trichloromethyl)pyrimidin-4-one **2e** was obtained in 40% yield together with the 4-(propanoyloxy)-2-(trichloromethyl)pyrimidine **2f** in 30% yield.



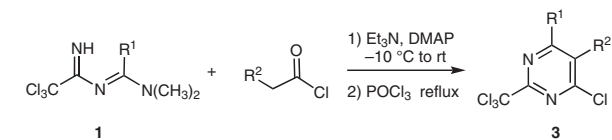
Scheme 1 Synthesis of 2-(trichloromethyl)pyrimidin-4-ones **2** from acyl chlorides

We believe that this cyclization process does not involve a concerted [4+2] cycloaddition process between the 1,3-diazadiene **1** and the ketenes because it is accelerated by DMAP. Possibly, it involves the formation of a key intermediate the *N*-acyl-1,3-diazadienium **A** (Scheme 2), followed by immediate intramolecular cyclization to form the intermediate **B**, which eliminates dimethylamine, which reacts with the acyl chloride to form the corresponding *N,N*-dimethylamide, to finally deliver the 2-(trichloromethyl)pyrimidin-4-one **2** and the respective 4-(acyloxy)-2-(trichloromethyl)pyrimidine.



Scheme 2 Possible mechanism in the acylation/intramolecular cyclization reaction of 2-(trichloromethyl)-1,3-diazadienes **1** with an acyl chloride

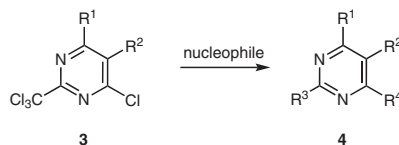
The moderate yields in the acylation/intramolecular cyclization process to produce 2-(trichloromethyl)pyrimidin-4-ones **2** are presumably due to the tedious purification of the samples, since the removal of the excess carboxylic acid generated by the hydrolysis (work up or on the silica gel chromatographic purification) led to material loss. Since our main interest was the synthesis of tetrachloropyrimidines **3**, as an alternative it was thought that pyrimidin-4-ones **2** might react with POCl_3 ³⁶ to give the corresponding tetrachloropyrimidine **3**. Therefore, we opted not to isolate the 2-(trichloromethyl)pyrimidin-4-one **2** and directly performed the chlorination reaction. Thus, the crude material obtained was reacted with POCl_3 (10.0 equiv) overnight in refluxing toluene solution, to form the 4-chloro-2-(trichloromethyl)pyrimidines **3a–j** (Table 1). 4-Chloro-2-(trichloromethyl)pyrimidines **3a** and **3b** were obtained in good yields when the acyl chloride was phenylacetyl chloride (entries 1 and 2). Lower yields were obtained when acetyl chloride was used as the acylating agent (entries 3 and 4). However, yields increased slightly when propanoyl chloride was utilized (entries 5 and 6). Yields were generally lower when the acylating agent was an α -haloacetyl chloride (entries 7–10), but yields were slightly higher when the 1,3-diazadiene installed a methyl group on C-4 (entries 8 and 10).

Table 1 Synthesis of 4-Chloro-2-(trichloromethyl)pyrimidines^a

Entry	3	R ¹	R ²	Yield (%)
1	3a	H	Ph	85
2	3b	CH ₃	Ph	70
3	3c	H	H	53
4	3d	CH ₃	H	57
5	3e	H	CH ₃	70
6	3f	CH ₃	CH ₃	64
7	3g	H	Cl	35
8	3h	CH ₃	Cl	50
9	3i	H	Br	21
10	3j	CH ₃	Br	40

^a Reaction conditions: 1. **1** (1.0 equiv), acyl chloride (2.2 equiv), Et₃N (2.2 equiv), DMAP (10 mol%), CH₂Cl₂, -10 °C to rt; 2. POCl₃ (10.0 equiv), toluene, reflux, overnight.

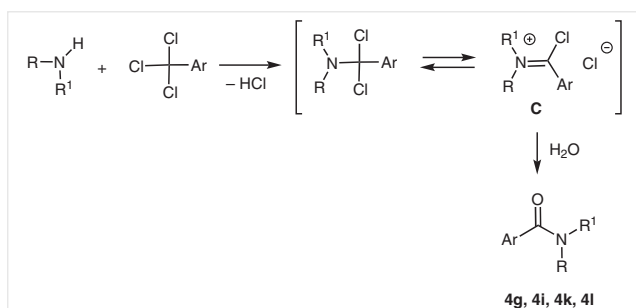
On the other hand, the chlorine substituent at C-4 and the trichloromethyl at C-2 in this type of pyrimidines **3** should be quite reactive principally in substitution reactions and could be used as congeners of various other pyrimidines.^{37–40} We studied their reactivity through substitution reactions with a variety of nucleophiles including, oxygen, sulfur, nitrogen, and carbon, giving the expected substitution products (Table 2). In all substitution reactions, we observed selective attack by the nucleophile at the more electrophilic carbon of the heterocyclic ring (C-4) according to a S_NAr2 mechanism, at low or at room temperature, without affecting the trichloromethyl group (entries 1, 3, 4, 6, 8, 10, and 13–16). However, when the nucleophile was oxygen and the tetrachloropyrimidine **3a** was reacted with an excess of sodium methoxide in methanol at 65 °C, dimethoxypyrimidine **4b** was formed possibly by the loss of trichloromethanide (entry 2). In sharp contrast, when sodium phenoxide is used, only the monosubstitution product **4c** was formed even when the tetrachloropyrimidine **3a** was heated at 65 °C overnight, this result is possibly due to its minor nucleophilic character compared with methoxide ion

Table 2 Substitution Reactions

Entry	3	Nucleophile (equiv)	Solvent	Temp (°C)	4	R ¹	R ²	R ³	R ⁴	Yield (%)
1	3a	NaOCH ₃ (10)	CH ₃ OH	rt	4a	H	Ph	CCl ₃	OCH ₃	63
2	3a	NaOCH ₃ (10)	CH ₃ OH	65	4b	H	Ph	OCH ₃	OCH ₃	86
3	3a	NaOPh (10)	THF	65	4c	H	Ph	CCl ₃	OPh	89
4	3a	NaSPh (2)	THF	-78	4d	H	Ph	CCl ₃	SPh	86 ⁴²
5	3a	NaSPh (10)	THF	rt	4e	H	Ph	CH(SPh) ₂	SPh	83
6	3a	BuNH ₂ (10)	CH ₂ Cl ₂	rt	4f	H	Ph	CCl ₃	NHBu	86
7	3a	BuNH ₂ (15)	CH ₂ Cl ₂	rt	4g	H	Ph	C(O)NHBu	NHBu	81
8	3b	BuNH ₂ (10)	CH ₂ Cl ₂	rt	4h	CH ₃	Ph	CCl ₃	NHBu	73
9	3b	BuNH ₂ (20)	CH ₂ Cl ₂	rt	4i	CH ₃	Ph	C(O)NHBu	NHBu	65
10	3a	morpholine (10)	CH ₂ Cl ₂	rt	4j	H	Ph	CCl ₃		83
11	3a	morpholine (14)	CH ₂ Cl ₂	rt	4k	H	Ph			80
12	3a	BnNH ₂ (5)	CH ₂ Cl ₂	rt	4l	H	Ph	CONHBn	NHBn	94
13	3a	NaN ₃ (5)	DMF	rt	4m	H	Ph	CCl ₃	N ₃	88
14	3d	NaN ₃ (5)	DMF	rt	4n	CH ₃	H	CCl ₃	N ₃	54
15	3a	NaCH(CO ₂ Et) ₂ (5)	THF	65	4o	H	Ph	CCl ₃	CH(CO ₂ Et) ₂	86
16	3a	KCN (5)	DMF	rt	4p	H	Ph	CCl ₃	CN	57

(entry 3). When an excess of sodium thiophenolate was reacted with tetrachloropyrimidine **3a** at room temperature, reduction of the trichloromethyl group took place,⁴¹ giving the thioketal **4e** in very good yield (entry 5).

It is noteworthy that the substitution reaction of these kinds of tetrachloropyrimidine **3** using a large excess of primary or secondary amine as the nucleophile results in the transformation of the trichloromethyl group into the respective amide, forming **4g**, **4i**, **4k**, and **4l** (entries 7, 9, 11, and 12). These products are presumably derived from the corresponding attack by the nitrogen atom on the trichloromethyl group to give the iminium salt **C** after chloride elimination, the hydrolysis of this intermediate **C** by the water present or on workup through the mechanism showed in Scheme 3 affords the corresponding amide. It is important to note, that the above reactions could be characteristic of all tetrachloropyrimidines **3** prepared in this way and are not restricted merely to **3a** or **3b**.



Scheme 3 Possible mechanism on reactivity of amines with trichloromethyl group

In summary, we have developed a new methodology for the preparation of 4-chloro-2-(trichloromethyl)pyrimidines **3** in a very efficient way from simple and accessible starting materials. We believe that this methodology is probably through acylation/intramolecular cyclization mechanism and should be of general interest. This synthetic strategy exhibits considerable structural flexibility that can be applied to a variety of acyl chlorides with one α -substituted group. The reactivity of these 4-chloro-2-(trichloromethyl)pyrimidines **3** was studied with a variety of nucleophilic species to give substituted products, which could be a useful tool for the construction of a variety of pyrimidines derivatives containing the trichloromethyl unit. Interestingly; we observed that the second attack depends of the nucleophile used. More reactive oxygen-derived nucleophiles (methoxide vs phenoxide ions) react on the heterocyclic ring through an S_NAr2 mechanism. While nitrogen and sulfur nucleophiles react directly on the trichloromethyl group probably because of the softness and hardness principle of these two elements.

All reactions were carried out in oven-dried round-bottom flasks under N_2 atmosphere. Reagents were purchased from Aldrich and used without treatment, unless otherwise indicated. NaH 60% dispersion in mineral oil. CH_2Cl_2 was distilled from CaH_2 under N_2 . 1H and ^{13}C NMR were recorded using Bruker (300 MHz) Avance 300 and Varian (500 MHz) Avance 500 instruments; 1H NMR relative to TMS ($\delta = 0.0$ ppm) and ^{13}C NMR using $CDCl_3$ ($\delta = 77.0$ ppm) as internal reference. LR-MS were obtained on an Shimadzu, GCLRMS-QP20.010 Plus mass spectrometer. Melting points were measured in a Mel-Temp II instrument and are uncorrected.

4-Chloro-2-(trichloromethyl)pyrimidines **3**; General Procedure

Under N_2 atmosphere, the crude 2-(trichloromethyl)-1,3-diazadiene **1** (1.0 equiv) in anhyd CH_2Cl_2 (10.0 mL) was cooled to -10 °C and Et_3N (2.2 equiv) was added. The respective acyl chloride (2.2 equiv) was added slowly followed by DMAP (10 mol%). The mixture was stirred at this temperature for 3 h, and then warmed to r.t. over 5 h. The reaction was quenched by the addition of sat. aq NH_4Cl (10.0 mL) and the product was extracted with CH_2Cl_2 (3×10.0 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. The crude product was suspended in toluene (10.0 mL), $POCl_3$ (5.0 mL, 53.5 mmol) was added and the mixture was heated at reflux temperature for 12 h. The excess $POCl_3$ was neutralized by the addition of sat. aq $NaHCO_3$ and the product was extracted with CH_2Cl_2 (3×30.0 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. The product was purified by flash chromatography (silica gel, hexanes/EtOAc).

4-Chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**)

Purification by column chromatography (hexanes/EtOAc 9:1) gave the product (262 mg, 85%) as a white solid. Recrystallization (hexanes/ CH_2Cl_2) gave pure **3a**; mp 153–154 °C.

1H NMR (300 MHz, $CDCl_3$): $\delta = 8.71$ (s, 1 H), 7.47–7.44 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.1, 160.0, 158.5, 134.7, 132.5, 129.7, 129.2, 129.0, 95.2$.

MS (EI): m/z (%) = 306 (M^+ , 56), 308 ($M^+ + 2$, 70), 310 ($M^+ + 4$, 34), 312 ($M^+ + 6$, 8), 275 (100).

HRMS (ESI+): m/z [$M + H$]⁺ calcd for $C_{11}H_7Cl_4N_2$: 306.9363; found: 306.9356.

4-Chloro-6-methyl-5-phenyl-2-(trichloromethyl)pyrimidine (**3b**)

Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (225 mg, 70%) as a white solid. Recrystallization (hexanes/ CH_2Cl_2) gave pure **3b**; mp 100–101 °C.

1H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$ – 7.51 (m, 3 H), 7.28–7.26 (m, 2 H), 2.46 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.2, 168.8, 167.0, 133.8, 133.6, 129.11, 129.06, 128.8, 95.9, 23.8$.

MS (EI): m/z (%) = 320.0 (M^+ , 13), 322 ($M^+ + 2$, 16), 324 ($M^+ + 4$, 8), 326 ($M^+ + 6$, 2), 285 (100).

4-Chloro-2-(trichloromethyl)pyrimidine (**3c**)

Purification by column chromatography (hexanes/EtOAc 9:1) gave the product (123 mg, 53%) as a yellow oil.

1H NMR (300 MHz, $CDCl_3$): $\delta = 8.79$ (d, $J = 5.4$ Hz, 1 H), 7.44 (d, $J = 5.4$ Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.0, 162.3, 158.7, 122.0, 92.2$.

MS (EI): m/z (%) = 230 (M^+ , 28), 232 (M^+ + 2, 36), 234 (M^+ + 4, 17), 236 (M^+ + 6, 4), 197 (100).

4-Chloro-6-methyl-2-(trichloromethyl)pyrimidine (3d)

Purification by column chromatography (hexanes/EtOAc 9:1) gave the product (140 mg, 57%) as a white solid. Recrystallization (hexanes/ CH_2Cl_2) gave pure **3d**; mp 58–59 °C.

^1H NMR (300 MHz, CDCl_3): δ = 7.27 (s, 1 H), 2.65 (s, 3 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 170.3, 165.4, 161.8, 121.0, 95.5, 24.0.

MS (EI): m/z (%) = 244 (M^+ , 21), 246 (M^+ + 2, 26), 248 (M^+ + 4, 13), 250 (M^+ + 6, 3), 213 (100).

4-Chloro-5-methyl-2-(trichloromethyl)pyrimidine (3e)

Purification by column chromatography (hexanes/EtOAc 9:1) gave the product (173 mg, 70%) as a white solid. Recrystallization (hexanes/ CH_2Cl_2) gave pure **3e**; mp 75–76 °C.

^1H NMR (300 MHz, CDCl_3): δ = 8.66 (s, 1 H), 2.46 (s, 3 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 163.7, 161.8, 158.4, 131.0, 99.9, 16.3.

MS (EI): m/z (%) = 244 (M^+ , 27), 246 (M^+ + 2, 38), 248 (M^+ + 4, 19), 250 (M^+ + 6, 4), 211 (100).

4-Chloro-5,6-dimethyl-2-(trichloromethyl)pyrimidine (3f)

Purification by column chromatography (hexanes/EtOAc 9:1) gave the product (167 mg, 64%) as a white solid. Recrystallization (hexanes/ CH_2Cl_2) gave pure **3f**; mp 95–96 °C.

^1H NMR (300 MHz, CDCl_3): δ = 2.65 (s, 3 H), 2.44 (s, 3 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 168.5, 162.2, 161.1, 128.7, 95.6, 23.2, 15.1.

MS (EI): m/z (%) = 258 (M^+ , 6), 260 (M^+ + 2, 7), 262 (M^+ + 4, 3), 264 (M^+ + 6, 2), 223 (100).

4,5-Dichloro-2-(trichloromethyl)pyrimidine (3g)

Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (93 mg, 35%) as a pale yellow solid. Recrystallization (hexanes/ CH_2Cl_2) gave pure **3g**; mp 69–70 °C.

^1H NMR (300 MHz, CDCl_3): δ = 8.83 (s, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 163.2, 159.3, 157.3, 130.7, 91.9.

MS (EI): m/z (%) = 264 (M^+ , 51), 266 (M^+ + 2, 77), 268 (M^+ + 4, 52), 270 (M^+ + 6, 16), 272 (M^+ + 8, 2), 170 (100).

4,5-Dichloro-6-methyl-2-(trichloromethyl)pyrimidine (3h)

Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (141 mg, 50%) as a pale yellow solid. Recrystallization (hexanes/ CH_2Cl_2) gave pure **3h**; mp 49–50 °C.

^1H NMR (300 MHz, CDCl_3): δ = 2.77 (s, 3 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 167.8, 161.8, 159.0, 129.6, 94.9, 23.4.

MS (EI): m/z (%) = 278 (M^+ , 26), 280 (M^+ + 2, 38), 282 (M^+ + 4, 27), 284 (M^+ + 6, 9), 286 (M^+ + 8, 2), 246 (100).

5-Bromo-4-chloro-2-(trichloromethyl)pyrimidine (3i)

Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (65 mg, 21%) as a pale yellow solid. Recrystallization (hexanes/ CH_2Cl_2) gave pure **3i**; mp 70–71 °C.

^1H NMR (300 MHz, CDCl_3): δ = 8.94 (s, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 164.0, 160.2, 157.3, 121.0, 99.9.

MS (EI): m/z (%) = 308 (M^+ , 9), 310 (M^+ + 2, 21), 312 (M^+ + 4, 17), 314 (M^+ + 6, 8), 316 (M^+ + 8, 2), 277 (100).

5-Bromo-4-chloro-6-methyl-2-(trichloromethyl)pyrimidine (3j)

Purification by column chromatography (hexanes/EtOAc 97.5:2.5) gave the product (130 mg, 40%) as a pale yellow oil.

^1H NMR (300 MHz, CDCl_3): δ = 2.81 (s, 3 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 169.9, 167.8, 162.7, 121.4, 94.9, 26.0.

MS (EI): m/z (%) = 322 (M^+ , 3), 324 (M^+ + 2, 6), 326 (M^+ + 4, 5), 328 (M^+ + 6, 2), 289 (100).

4-Methoxy-5-phenyl-2-(trichloromethyl)pyrimidine (4a)

Under N_2 atmosphere, anhyd CH_3OH (3.0 mL, 74.63 mmol) was added to a flask containing Na (128 mg, 10.0 equiv, 5.57 mmol) and the mixture was stirred for 5 min. 4-Chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 154 mg, 1.0 equiv, 0.5 mmol) was added and the mixture was stirred at rt overnight. After completion, the mixture was neutralized with aq 5% AcOH, EtOAc (30.0 mL) was added, the mixture was washed with sat. NH_4Cl solution, and the product was extracted with EtOAc (2 \times 20.0 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (96 mg, 63%) as a pale yellow oil.

^1H NMR (300 MHz, CDCl_3): δ = 8.52 (s, 1 H), 7.50–7.49 (m, 2 H), 7.42–7.36 (m, 3 H), 4.04 (s, 3 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 166.7, 163.4, 156.1, 131.8, 129.0, 128.9, 128.6, 122.2, 96.3, 54.7.

MS (EI): m/z (%) = 302 (M^+ , 28), 304 (M^+ + 2, 26), 306 (M^+ + 4, 9), 267 (100).

2,4-Dimethoxy-5-phenylpyrimidine (4b)

Under N_2 atmosphere, anhyd CH_3OH (3.0 mL, 74.63 mmol) was added to a flask containing Na (127 mg, 10.0 equiv, 5.51 mmol) and the mixture was stirred for 5 min. 4-Chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 160 mg, 1.0 equiv, 0.52 mmol) was added and the mixture was heated to 65 °C overnight. After completion, the mixture was neutralized with aq 5% AcOH, EtOAc (30.0 mL) was added, the mixture was washed with sat. NH_4Cl solution, and the product was extracted with EtOAc (2 \times 20.0 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. Purification by column chromatography (hexanes/EtOAc 85:15) gave the product (97 mg, 86%) as a white solid; mp 57–58 °C (hexanes/ CH_2Cl_2).

^1H NMR (300 MHz, CDCl_3): δ = 8.19 (s, 1 H), 7.43–7.41 (m, 2 H), 7.37–7.34 (m, 2 H), 7.30–7.27 (m, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 168.2, 164.4, 157.5, 133.2, 128.8, 128.4, 127.7, 116.2, 54.8, 54.1.

MS (EI): m/z (%) = 216 (M^+ , 100), 201 (M^+ – 15, 39), 186 (M^+ – 30, 70).

4-Phenoxy-5-phenyl-2-(trichloromethyl)pyrimidine (4c)

Under N_2 atmosphere, 75% NaH (131 mg, 10.0 equiv, 4.07 mmol) was suspended in THF (5.0 mL), 85% phenol (544 mg, 10.0 equiv, 4.9 mmol) was added, and the mixture was stirred for 10 min. Subsequently, 4-chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 124 mg, 1.0 equiv, 0.4 mmol) was added. The mixture was heated to 65 °C overnight. After completion, EtOAc (30.0 mL) was added, the mixture was washed with sat. NH_4Cl solution, and the product was extracted with EtOAc (2 \times 20.0 mL). The combined organic extracts were dried

(Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (130 mg, 89%) as a white solid; mp 108–109 °C (hexanes/CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃): δ = 8.70 (s, 1 H), 7.67–7.64 (m, 2 H), 7.50–7.41 (m, 3 H), 7.38–7.32 (m, 2 H), 7.19–7.18 (m, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 165.9, 163.4, 157.8, 152.1, 131.6, 129.4, 129.18, 129.15, 128.9, 125.7, 122.6, 121.5, 95.9.

MS (EI): *m/z* (%) = 364 (M⁺, 70), 366 (M⁺ + 2, 68), 368 (M⁺ + 4, 27), 85 (100).

2-[Bis(phenylthio)methyl]-5-phenyl-4-(phenylthio)pyrimidine (4e)

Under N₂ atmosphere, 60% NaH (197 mg, 10.0 equiv, 4.91 mmol) was suspended in THF (10.0 mL), thiophenol (0.55 mL, 10.0 equiv, 5.21 mmol) was added. Subsequently, 4-chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 161 mg, 1.0 equiv, 0.52 mmol) was added and the mixture was stirred at rt overnight. After completion, EtOAc (30.0 mL) was added, the mixture was washed with sat. NH₄Cl solution, and the product was extracted with EtOAc (2 × 20.0 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (213 mg, 83%) as a yellow solid; mp 78–79 °C (hexanes/CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃): δ = 8.22 (s, 1 H), 7.42 (s, 5 H), 7.32–7.29 (m, 5 H), 7.26–7.22 (m, 5 H), 7.17–7.14 (m, 5 H), 5.36 (s, 1 H).

¹³C NMR (75 MHz, CDCl₃): δ = 168.2, 165.8, 154.7, 152.7, 135.6, 134.1, 134.0, 132.4, 131.3, 130.7, 129.2, 129.1, 129.0, 128.89, 128.86, 128.7, 128.4, 127.7, 127.4, 124.2, 124.0, 117.8, 110.9, 62.6.

MS (EI): *m/z* (%) = 494 (M⁺), 384 (M⁺ – 110, 53), 355 (M⁺ – 139, 70), 274 (100).

N-Butyl-5-phenyl-2-(trichloromethyl)pyrimidin-4-amine (4f)

Under N₂ atmosphere, 4-chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 156 mg, 1.0 equiv, 0.51 mmol) was dissolved in anhyd CH₂Cl₂ (3.0 mL), BuNH₂ (0.5 mL, 10 equiv, 5.05 mmol) was added, and the mixture was stirred at rt overnight. After completion, CH₂Cl₂ (30.0 mL) was added, the mixture was washed with sat. NaCl solution, and the product was extracted with CH₂Cl₂ (2 × 20.0 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (152 mg, 86%) as a white solid; mp 86–87 °C (hexanes/CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃): δ = 8.06 (s, 1 H), 7.46–7.31 (m, 5 H), 5.24 (br s, 1 H), 3.46 (q, *J* = 6.9 Hz, 2 H), 1.51 (quint, *J* = 6.9 Hz, 2 H), 1.28 (sext, *J* = 7.2 Hz, 2 H), 0.86 (t, *J* = 7.2 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 163.8, 160.1, 152.9, 133.2, 129.7, 129.0, 128.6, 118.9, 97.2, 40.9, 31.2, 20.0, 13.8.

MS (EI): *m/z* (%) = 343 (M⁺, 32), 345 (M⁺ + 2, 30), 347 (M⁺ + 4, 12), 288 (100).

N-Butyl-4-(butylamino)-5-phenylpyrimidine-2-carboxamide (4g)

Under N₂ atmosphere, to a solution of 4-chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 155 mg, 1.0 equiv, 0.5 mmol) in anhyd CH₂Cl₂ (3.0 mL), BuNH₂ (0.75 mL, 15.0 equiv, 7.58 mmol) was added, and the mixture was stirred at rt overnight. After completion, CH₂Cl₂ (30.0 mL) was added, the mixture was washed with sat. NaCl solution, and the product was extracted with CH₂Cl₂ (2 × 20.0 mL). The com-

binated organic extracts were dried (Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (EtOAc) gave the product (132 mg, 81%) as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ = 8.12 (s, 1 H), 7.97 (br s, 1 H), 7.54–7.43 (m, 3 H), 7.39–7.36 (m, 2 H), 5.18 (br s, 1 H), 3.56–3.46 (m, 4 H), 1.66–1.53 (m, 4 H), 1.47–1.33 (m, 4 H), 0.99–0.93 (m, 6 H).

¹³C NMR (75 MHz, CDCl₃): δ = 163.0, 159.7, 156.5, 153.5, 133.6, 129.5, 128.8, 128.5, 120.2, 40.7, 39.3, 31.6, 31.3, 20.0, 13.7.

MS (EI): *m/z* (%) = 326 (M⁺), 297 (M⁺ – 29, 49), 227 (M⁺ – 99, 75), 269 (100).

N-Butyl-6-methyl-5-phenyl-2-(trichloromethyl)pyrimidin-4-amine (4h)

Under N₂ atmosphere, 4-chloro-6-methyl-5-phenyl-2-(trichloromethyl)pyrimidine (**3b**; 162 mg, 1.0 equiv, 0.53 mmol) was dissolved in anhyd CH₂Cl₂ (3.0 mL), BuNH₂ (0.5 mL, 10.0 equiv, 5.05 mmol) was added, and the mixture was stirred at rt overnight. After completion, CH₂Cl₂ (30.0 mL) was added, the mixture was washed with sat. NaCl solution, and the product was extracted with CH₂Cl₂ (2 × 20.0 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (139 mg, 73%) as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ = 7.48–7.35 (m, 3 H), 7.19–7.15 (m, 2 H), 4.58 (br s, 1 H), 3.37 (q, *J* = 6.9 Hz, 2 H), 2.13 (s, 3 H), 1.42 (q, *J* = 7.2 Hz, 2 H), 1.26–1.18 (m, 2 H), 0.85–0.80 (t, *J* = 7.2 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 163.2, 161.5, 160.8, 133.8, 129.8, 129.5, 128.6, 117.0, 97.8, 40.9, 31.4, 22.3, 19.9, 13.8.

N-Butyl-4-(butylamino)-6-methyl-5-phenylpyrimidine-2-carboxamide (4i)

Under N₂ atmosphere, 4-chloro-6-methyl-5-phenyl-2-(trichloromethyl)pyrimidine (**3b**; 125 mg, 1.0 equiv, 0.39 mmol) was dissolved in anhyd CH₂Cl₂ (3.0 mL), BuNH₂ (0.75 mL, 20.0 equiv, 7.58 mmol) was added, and the mixture was stirred at rt overnight. After completion, CH₂Cl₂ (30.0 mL) was added, the mixture was washed with sat. NaCl solution, and the product was extracted with CH₂Cl₂ (2 × 20.0 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (hexanes/EtOAc 1:1) gave the product (86 mg, 65%) as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ = 7.96 (br s, 1 H), 7.47–7.37 (m, 3 H), 7.15–7.12 (m, 2 H), 4.47 (br s, 1 H), 3.45–3.33 (m, 4 H), 2.12 (s, 3 H), 1.58–1.51 (m, 2 H), 1.44–1.35 (m, 2 H), 1.26–1.18 (m, 2 H), 0.89 (t, *J* = 7.2 Hz, 3 H), 0.82 (t, *J* = 7.2 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 163.4, 161.3, 160.4, 155.7, 133.9, 129.7, 129.4, 129.2, 128.5, 119.3, 118.4, 115.6, 40.8, 39.3, 31.6, 31.4, 22.2, 20.1, 20.0, 13.7.

MS (EI): *m/z* (%) = 340 (M⁺), 311 (M⁺ – 29, 93), 240 (M⁺ – 100, 67), 115 (100).

4-Morpholino-5-phenyl-2-(trichloromethyl)pyrimidine (4j)

Under N₂ atmosphere, 4-chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 168 mg, 1.0 equiv, 0.55 mmol) was dissolved in anhyd CH₂Cl₂ (3.0 mL), morpholine (0.5 mL, 10.0 equiv, 5.7 mmol) was added, and the mixture was stirred at rt overnight. After completion, CH₂Cl₂ (30.0 mL) was added, the mixture was washed with sat. NaCl solution, and the product was extracted with CH₂Cl₂ (2 × 20.0 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under

vacuum. Purification by column chromatography (hexanes/EtOAc 9:1) gave the product (164 mg, 83%) as a white solid; mp 101–102 °C (hexanes/CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃): δ = 8.27 (s, 1 H), 7.51–7.40 (m, 5 H), 3.64–3.61 (m, 4 H), 3.44–3.41 (m, 4 H).

¹³C NMR (75 MHz, CDCl₃): δ = 162.9, 161.3, 158.0, 136.2, 129.2, 128.4, 127.62, 127.57, 120.1, 97.0, 66.2, 47.4.

MS (EI): *m/z* (%) = 357 (M⁺, 42), 359 (M⁺ + 2, 39), 361 (M⁺ + 4, 15), 321 (100).

4-Morpholino-2-(morpholinocarbonyl)-5-phenylpyrimidine (4k)

Under N₂ atmosphere, 4-chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 162 mg, 1.0 equiv, 0.53 mmol) was dissolved in anhyd CH₂Cl₂ (3.0 mL), morpholine (0.65 mL, 14.0 equiv, 7.42 mmol) was added, and the mixture was stirred at rt overnight. After completion, CH₂Cl₂ (30.0 mL) was added, the mixture was washed with sat. NaCl solution, and the product was extracted with CH₂Cl₂ (2 × 20.0 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (EtOAc) gave the product (150 mg, 80%) as a white solid; mp 112–113 °C (hexanes/CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃): δ = 8.19 (s, 1 H), 7.46–7.39 (m, 5 H), 3.82 (br s, 4 H), 3.73–3.70 (m, 2 H), 3.60–3.58 (m, 4 H), 3.51–3.50 (m, 2 H), 3.36–3.34 (m, 4 H).

¹³C NMR (75 MHz, CDCl₃): δ = 165.7, 161.7, 159.2, 157.5, 136.7, 129.2, 128.3, 127.5, 120.7, 66.8, 66.6, 66.3, 47.4, 47.2, 42.1.

MS (EI): *m/z* (%) = 354 (M⁺), 183 (M⁺ – 171, 33), 56 (M⁺ – 298, 25), 241 (100).

N-Benzyl-4-(benzylamino)-5-phenylpyrimidine-2-carboxamide (4l)

Under N₂ atmosphere, 4-chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 157 mg, 1.0 equiv, 0.51 mmol) was dissolved in anhyd CH₂Cl₂ (3.0 mL), BnNH₂ (0.3 mL, 5.0 equiv, 2.74 mmol) was added and the mixture was stirred at rt overnight. After completion, CH₂Cl₂ (30.0 mL) was added, the mixture was washed with sat. NaCl solution, and the product was extracted with CH₂Cl₂ (2 × 20.0 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (EtOAc) gave the product (189 mg, 94%) as a yellow solid; mp 133–134 °C (hexanes/CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃): δ = 8.14 (s, 1 H), 7.39–7.22 (m, 15 H), 5.74 (br s, 1 H), 4.66–4.60 (m, 4 H).

¹³C NMR (75 MHz, CDCl₃): δ = 162.8, 159.3, 156.1, 153.8, 138.1, 138.0, 133.2, 129.5, 128.8, 128.5, 128.5, 128.4, 127.6, 127.3, 127.2, 127.1, 120.5, 45.0, 43.5.

MS (EI): *m/z* (%) = 394 (M⁺), 261 (M⁺ – 133, 33), 106 (M⁺ – 288, 24), 91 (100).

4-Azido-5-phenyl-2-(trichloromethyl)pyrimidine (4m)

Under N₂ atmosphere, 4-chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 165 mg, 1.0 equiv, 0.54 mmol) was dissolved in anhyd DMF (3.0 mL), NaN₃ (188 mg, 5.0 equiv, 2.89 mmol) was added and the mixture was stirred at rt overnight. After completion, EtOAc (30.0 mL) was added, the mixture was washed with sat. NaCl solution, and the product was extracted with EtOAc (2 × 20.0 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (150 mg, 88%) as a white solid; mp 84–85 °C (hexanes/CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃): δ = 8.70 (s, 1 H), 7.53–7.48 (m, 5 H).

¹³C NMR (75 MHz, CDCl₃): δ = 163.6, 160.1, 157.9, 131.5, 129.3, 129.0, 128.96, 128.90, 128.80, 124.5, 95.7.

MS (EI): *m/z* (%) = 313 (M⁺, 6), 315 (M⁺ + 2, 5), 317 (M⁺ + 4, 2), 250 (100).

4-Azido-6-methyl-2-(trichloromethyl)pyrimidine (4n)

Under N₂ atmosphere, 4-chloro-6-methyl-2-(trichloromethyl)pyrimidine (**3d**; 246 mg, 1.0 equiv, 1 mmol) was dissolved in anhyd DMF (3.0 mL), NaN₃ (330 mg, 5.0 equiv, 5.0 mmol) was added, and the mixture was stirred at rt overnight. After completion, EtOAc (30.0 mL) was added, the mixture was washed with sat. NaCl solution, and the product was extracted with EtOAc (2 × 20.0 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (136 mg, 54%) as a colorless oil.

¹H NMR (300 MHz, CDCl₃): δ = 6.58 (s, 1 H), 2.51 (s, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 170.1, 164.9, 163.0, 109.3, 96.1, 24.1.

MS (EI): *m/z* (%) = 251 (M⁺, 51), 253 (M⁺ + 2, 49), 255 (M⁺ + 4, 17), 190 (100).

Diethyl 2-[5-Phenyl-2-(trichloromethyl)pyrimidin-4-yl]malonate (4o)

Under N₂ atmosphere, 60% NaH (114 mg, 10.0 equiv, 2.85 mmol) was suspended in THF (15.0 mL), diethyl malonate (0.4 mL, 5.0 equiv, 2.62 mmol) was added and the mixture was stirred for 10 min. Subsequently, 4-chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 157 mg, 1.0 equiv, 0.51 mmol) was added. The mixture was stirred and heated to 65 °C overnight. After completion, EtOAc (30.0 mL) was added, the mixture was washed with sat. NH₄Cl solution, and the product was extracted with EtOAc (2 × 20.0 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (hexanes/EtOAc 95:5) gave the product (189 mg, 86%) as a white solid; mp 117–118 °C (hexanes/CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃): δ = 8.71 (s, 1 H), 7.45–7.42 (m, 3 H), 7.27–7.24 (m, 2 H), 4.94 (s, 1 H), 4.15–4.09 (m, 4 H), 1.14 (t, *J* = 7.2 Hz, 6 H).

¹³C NMR (75 MHz, CDCl₃): δ = 165.8, 163.9, 160.4, 158.1, 135.1, 133.2, 129.4, 129.1, 128.9, 96.1, 62.2, 57.7, 13.9.

MS (EI): *m/z* (%) = 432 (M⁺, 21), 434 (M⁺ + 2, 8), 436 (M⁺ + 4, 1), 358 (100).

5-Phenyl-2-(trichloromethyl)pyrimidine-4-carbonitrile (4p)

Under N₂ atmosphere, 4-chloro-5-phenyl-2-(trichloromethyl)pyrimidine (**3a**; 162 mg, 1.0 equiv, 0.53 mmol) was dissolved in anhyd DMF (3.0 mL), and 18-crown-6 (cat.) was added. Subsequently, KCN (179 mg, 5.0 equiv, 2.74 mmol) was added and the mixture was stirred at rt overnight. After completion, EtOAc (30.0 mL) was added, the mixture was washed with sat. NaCl solution, and the product was extracted with EtOAc (2 × 20.0 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under vacuum. Purification by column chromatography (hexanes/EtOAc 9:1) gave the product (90 mg, 57%) as a white solid; mp 132–133 °C (hexanes/CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃): δ = 9.09 (s, 1 H), 7.57–7.56 (d, *J* = 3.3 Hz, 5 H).

¹³C NMR (75 MHz, CDCl₃): δ = 164.6, 159.8, 138.9, 137.5, 131.0, 130.5, 129.7, 128.8, 114.4, 95.1.

MS (EI): *m/z* (%) = 297 (M⁺, 11), 299 (M⁺ + 2, 10), 301 (M⁺ + 4, 4), 262 (100).

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Supporting Information

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