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Chemoselective Reduction of Trichloromethyl Compounds to *gem*-Dichloromethyl Groups Following Appel's Reaction Protocol

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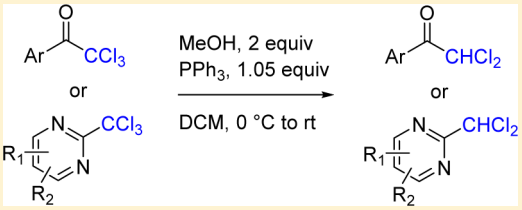
Supporting Information

ABSTRACT: A simple and easy reduction of trichloroacetyl compounds following the modification of Appel's reaction protocol, using triphenylphosphine and methanol, afforded the corresponding dichloroacetyl compounds, with the exception of trichloroacetylmorpholine, in yields of 80−98% under very mild experimental conditions. Likewise, when trichloromethyl heterocyclic compounds contain another reactive functional group, the reaction is highly chemoselective giving the dichloromethyl derivative.



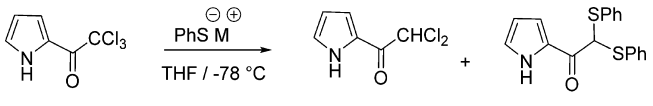
The *gem*-dichloromethyl group is an important structural framework present in a number of biologically active compounds such as antibiotics and diuretics.[1] Additionally, some dichloromethyl derivatives are also found to be important within the agrochemical field[2] and are well-known to be useful intermediates for the synthesis of heterocycles,[3] α,β-unsaturated ketones,[4] 1,4-diones,[5] ynols,[6] and cyclopropanes.[7] Likewise, they are widely used as synthetic precursors to afford the corresponding aldehydes under basic conditions[8] as well as precursors for *gem*-difluoromethyl groups by the double nucleophilic substitution of the chlorides by fluoride ions.[9]

General methods to prepare dichloromethyl compounds involve Lewis acid catalyzed acylation of arenes,[10] oxyhalogenation of alkynes,[11] and chlorination of ketones which implicates using different types of chlorine sources,[12] such as sulfuryl chloride,[13] thionyl chloride,[14] *N*-chlorosuccinimide,[15] and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH).[16] However, few methods have been described to allow the formation of *gem*-dichloromethyl compounds employing trichloromethyl derivatives as starting materials. In this context, *gem*-dichloromethyl compounds can be directly synthesized by a monodechlorination reaction of the corresponding trichloromethyl derivative via partial hydrogenation using a platinum on a carbon-catalyzed system.[17] Another attractive approach was demonstrated in the seminal work of Hall and co-workers, involving Grignard reagents as electron donors for 2,2,2-trichloro-1-arylethanones to synthesize substituted α,α-dichloroketones.[18] Unfortunately, these methods display limitations and disadvantages such as poor yields, use of high temperatures, side-product formation, and low chemoselectivity. Therefore, the preparation of these compounds with a more efficient, simple, and general route is highly desirable.

In 2007, while our research group was developing the synthesis of 2-substituted-1,3-dithianes from trichloromethyl compounds, we observed that the reaction of trichloroacetylpyrrole **1a** with 5 equiv of 1,3-propanodithiol and 3 equiv of sodium hydride in dry THF at −40 °C afforded a 71% yield of dichloroacetylpyrrole **2a**.[19] We envisioned that this protocol could be applicable to the development of a convenient one-pot procedure for a direct conversion of trichloromethyl compounds into the dichloromethyl derivatives.

We evaluated the reduction of trichloroacetyl compounds **1** in the presence of sulfur nucleophiles, using the 2-trichloroacetylpyrrole **1a** as a model. When **1a** was reacted with 2.0 equiv of sodium thiophenolate (generated from thiophenol and sodium hydride at room temperature) in THF at −78 °C, after 10 min, a mixture of the dichloroacetylpyrrole **2a** in 60% yield along with bis(phenylthio) compound **3a** in 20% yield was obtained (Scheme 1). The latter compound is

Scheme 1. Reduction of Trichloroacetylpyrrole with Thiophenolate



suggested to arise as a consequence of a substitution reaction of dichloroacetylpyrrole **2a** by the presence of the thiophenolate ion in the mixture reaction. An improved yield of **2a** (94%) was achieved employing 2.0 equiv of lithium thiophenolate (generated from thiophenol and *n*-BuLi) at −78 °C, and only traces of **3a** was observed.

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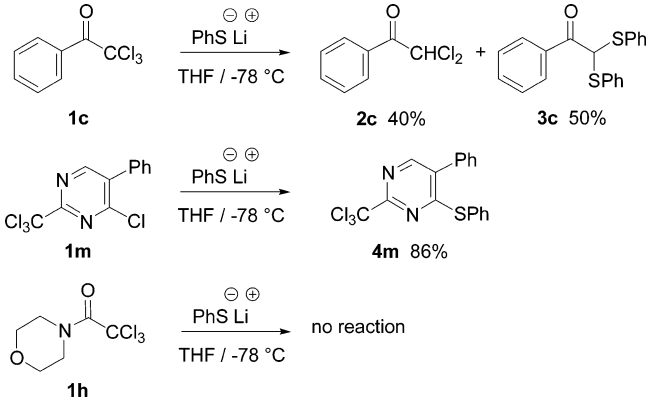
However, the application of this reduction process to trichloroacetophenone **1c** under the same conditions was less successful, affording dichloroacetophenone **2c**[17] in 40% yield along with the respective dithioacetal **3c** in 50% yield (Scheme 2). In fact, it is known that the dechlorination activity is

Scheme 2. Reduction Process of Trichloroacetyl Compounds 1 with Lithium Thiophenolate

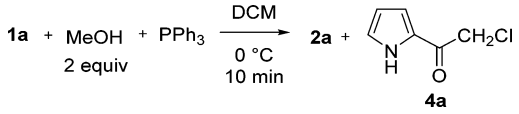


strongly influenced by the electronic environment of the substituents attached to the trichloromethyl group.[20] Another setback of this methodology was the poor chemoselectivity observed when trichloromethylpyrimidine **1m** was treated under similar conditions, giving the nucleophilic aromatic substitution product **4m** as the only isolable product in 86% yield which is possibly formed via a Meisenheimer intermediate. Furthermore, the trichloroacetylmorpholine **1h** did not react using the previous reduction conditions even under long periods of time.

In view of these results, we decided to explore another alternative to carry out the conversion of trichloromethyl compounds to *gem*-dichloromethyl derivatives. It is well documented that the treatment of alcohols with Appel's salt gives the corresponding halide, usually in very good yields.[21] Appel's salt can be formed by the reaction between 1 equiv of triphenylphosphine and 1 equiv of a tetrahalomethane such as CCl_4 or CBr_4. Mechanistically, 1 equiv of haloform is formed as a byproduct in this halogenation process. We reasoned that in this reaction, trichloromethyl compounds with an electron-withdrawing group **1** could be used instead of tetrahalomethanes to reduce tricholoromethyl compounds to *gem*-dichloromethyl derivatives **2**. Although, in 2011 the Gilheany group reported the synthesis of pentachloroacetone in moderate yield from hexachloroacetone under Appel's reaction conditions using 2-naphthol in toluene solution,[22] to date no systematic work has been published employing substrates containing other reactive functional groups, to demonstrate chemoselective reactivity and the potential use of this methodology to afford *gem*-dichloromethyl compounds from trichloromethyl derivatives. To examine this alternative, we next studied the reactivity of trichloromethyl compounds under Appel's reaction conditions in order to see if the reduction process occurs in these substrates. At the outset of our study, we used trichloroacetylpyrrole **1a** as a model to evaluate the reduction process in the presence of 2.0 equiv of methanol with different amounts of triphenylphosphine (Table 1).

When 1.2 equiv of triphenylphosphine were used, dichloroacetylpyrrole **2a** was obtained in 80% yield and chloroacetylpyrrole **4a** in 10% yield (Table 1, entry 1). The amount of triphenylphosphine was decreased to 1.0 equiv in an attempt to avoid the formation of the over-reduced chloroacetylpyrrole **4a**, affording dichloroacetylpyrrole **2a** in 89% yield and a trace amount of starting material. An appreciable change in the yield was observed when a slight excess of triphenylphosphine (1.05 equiv) was used (entry 3) to afford **2a** in 94% yield.

Table 1. Optimization of Reaction Conditions[a]

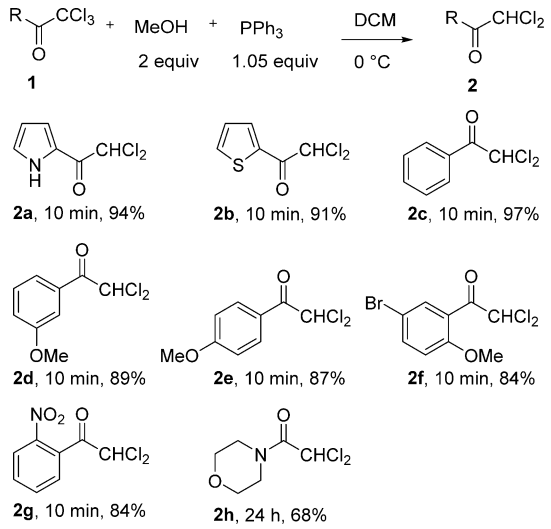


entry	PPh_3 (mmol)	**1a** (%)	**2a** (%)	**4a** (%)
1	1.2	0	80	10
2	1.0	trace	89	0
3	1.05	0	94	0

[a]Reaction conditions: **1a** (1.0 equiv, 1 mmol), MeOH (2.0 equiv), DCM (5.0 mL) under N_2 at 0 °C.

With the optimized reaction conditions in hand, this methodology for the generation of dichloromethyl derivatives **2** was extended. We first investigated the monodechlorination reaction of the more reactive trichloroacetyl derivatives **1b**−**1g** efficiently affording their corresponding *gem*-dichloroacetyl products **2b**−**2g** in high yields under short periods of time (Table 2). In contrast, although the trichloroacetylmorpholine **1h** was transformed into the dichloroacetylmorpholine **2h**[23] in acceptable yield (68%), the reaction period was longer (24 h). The distinct reactivity difference in time between **1h** and the trichloroacetyl compounds **1a**−**1g** could be a result of the corresponding electronic properties of **1h** which is slightly more electron-rich than **1a**−**1g**.

Table 2. Synthesis of Dichloroacetyl Compounds[a]



[a]Reaction conditions: **1a** (1.0 equiv, 1 mmol), MeOH (2.0 equiv), PPh_3 (1.05 equiv), DCM (5.0 mL) under N_2 at 0 °C.

Lastly, this reduction process was extrapolated to other trichloromethyl compounds containing other reactive functional groups such as **1j**−**1o**. Such derivatives afforded a highly chemoselective reduction, as is illustrated in dichloromethyl compounds **2j**−**2o** (Table 3). In each case, the corresponding dichloromethyl compound **2** was the exclusive product

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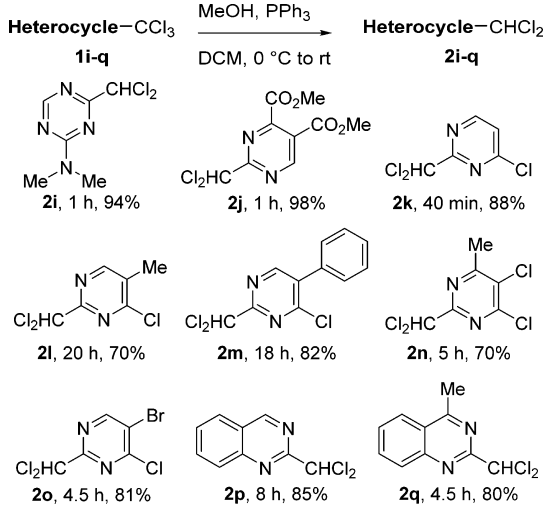
Table 3. Synthesis of Dichloromethyl Heterocyclic Compounds



[a]Reaction conditions: **1i−q** (1.0 equiv, 1 mmol), MeOH (2.0 equiv), PPh_3 (1.05 equiv), DCM (5.0 mL) under N_2 at 0 °C.

affording high yields under moderate periods of time, along with no significant nucleophilic displacement on C-4 or C-5 of the trichloromethylpyrimidines as when sodium/lithium thiophenolate was employed.

In summary, we have reported an efficient and simple procedure to prepare *gem*-dichloromethyl compounds using Appel's reaction conditions from trichloromethyl derivatives. This dechlorinantion reaction is found to be highly chemoselective and is expected to be particularly useful in those instances where the trichloromethyl compounds are the usual precursors of dichloromethyl derivatives which are not affordable in good yields by other routes.

EXPERIMENTAL SECTION

General. All moisture-sensitive reactions were carried out in oven-dried glassware under an argon atmosphere. Reagents were used without any further purification. Nuclear Magnetic Resonance (NMR) spectra were measured at 300 MHz. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) relative to Me_4Si (δ = 0.0 ppm) with coupling constants (J) reported in hertz (Hz). Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad singlet (bs).^{13}C NMR signals are reported using 77.0 ppm ($CDCl_3$) as the internal reference.

The 2-trichloroacetylpyrrole **1a** is commercially available, whereas the trichloromethyl compounds **1b−g**,[24] **1i−j**,[19] and **1p−q**[25] were easily synthesized in good yields according to literature methods. The trichloroacetylmorpholine **1h** was prepared from trichloroacetyl chloride and morpholine.

General Procedure for Synthesis of *gem*-Dichloromethyl Compounds (2). Under a nitrogen atmosphere, to a solution of the respective trichloromethyl compound **1** (1.0 mmol, 1.0 equiv) and methanol (80.0 μL, 2.0 mmol, 2.0 equiv) in anhydrous dichloromethane (3.0 mL) at 0 °C, a solution of triphenylphosphine (275 mg, 1.05 mmol, 1.05 equiv) in anhydrous dichloromethane (1.5 mL) was added dropwise at 0 °C. The reaction mixture was stirred for the time indicated in Tables 2 and 3. In the reactions that were more than 10 min, the temperature was allowed to rise to room temperature. After completion, the reaction was concentrated under *vacuum*. The desired dichloromethyl product **2** was purified through flash column chromatography on silica gel and eluted with hexane−EtOAc mixtures.

2-(Dichloroacetyl)pyrrol (2a).[17a] This compound was purified by flash column chromatography using hexanes−EtOAc (9:1) and obtained as a white solid (167 mg, 94% yield); crystallization (hexanes−CH_2Cl_2); mp 90−91 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.05 (brs, 1H), 7.24−7.22 (m, 1H), 7.20−7.17 (m, 1H), 6.52 (s, 1H), 6.38 (td, J = 4.2, 2.5 Hz, 1H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 177.0, 128.2, 126.0, 119.3, 111.8, 67.2. HRMS (ESI+): calcd for $C_6H_6Cl_2NO$ $[M + H]^+$ 177.9826, found 177.9823.

2-(Dichloroacetyl)thiopene (2b).[17b] This compound was purified by flash column chromatography using hexanes−EtOAc (98:2) and obtained as a pale yellow oil (177 mg, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (dd, 1H, J = 3.9, 1.2 Hz), 7.81 (dd, 1H, J = 4.9, 1.2 Hz), 7.21 (dd, 1H, J = 4.9, 3.9 Hz), 6.51 (s, 1H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 179.7, 137.0, 136.4, 134.8, 128.6, 67.9. HRMS (ESI+): calcd for $C_6H_5Cl_2OS$ $[M + H]^+$ 194.9438, found 194.9435.

Dichloroacetophenone (2c).[17a] This compound was purified by flash column chromatography using hexanes−EtOAc (98:2) and obtained as a colorless oil (183 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, 2H, J = 7.2 Hz), 7.65 (t, 1H, J = 7.5 Hz), 7.52 (t, 2H, J = 8.1 Hz), 6.70 (s, 1H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 185.9, 134.5, 131.3, 129.7, 128.9, 67.7. HRMS (ESI+): calcd for $C_8H_7Cl_2O$ $[M + H]^+$ 188.9874, found 188.9874.

3-Methoxy(dichloro)acetophenone (2d).[17a] This compound was purified by flash column chromatography using hexanes−EtOAc (9:1) and obtained as a yellow solid (195 mg, 89% yield); crystallization (hexanes−CH_2Cl_2); mp 37−39 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 7.8 Hz, 1H), 7.60−7.57 (m, 1H), 7.42 (t, 1H, J = 8.1 Hz), 7.19 (dd, 1H, J = 8.1, 2.1 Hz), 6.69 (s, 1H), 3.87 (s, 3H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 185.7, 159.9, 132.6, 129.8, 122.0, 121.1, 114.0, 67.7, 55.5. HRMS (ESI+): calcd for $C_9H_9Cl_2O_2$ $[M + H]^+$ 218.9979, found 218.9984.

4-Methoxy(dichloro)acetophenone (2e).[17a] This compound was purified by flash column chromatography using hexanes-EtOAc (9:1) and obtained as pale yellow oil (191 mg, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, 2H, J = 9 Hz), 6.98 (d, 2H, J = 9 Hz), 6.65 (s, 1H), 3.90 (s, 3H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 184.6, 164.6, 132.2, 123.9, 114.2, 67.8, 55.6. HRMS (ESI+): calcd for $C_9H_9Cl_2O_2$ $[M + H]^+$ 218.9979, found 218.9974.

5-Bromo-2-methoxy(dichloro)acetophenone (2f). This compound was purified by flash column chromatography using hexanes−EtOAc (9:1) and obtained as a white solid (250 mg, 84% yield); crystallization (hexanes−CH_2Cl_2); mp 86−87 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, 1H, J = 2.5 Hz), 7.61 (dd, 1H, J = 8.9, 2.5 Hz), 7.01 (s, 1H), 6.88 (d, 1H, J = 8.9 Hz), 3.94 (s, 3H). ^{13}C {1H} NMR (125 MHz, $CDCl_3$): δ 186.5, 157.3, 137.7, 134.6, 124.4, 113.8, 113.7, 70.6, 56.3. HRMS (ESI+): calcd for $C_9H_8BrCl_2O_2$ $[M + H]^+$ 298.9064, found 298.9072.

2-Nitro(dichloro)acetophenone (2g). This compound was purified by flash column chromatography using hexanes−EtOAc (9:1) and obtained as a pale yellow solid (197 mg, 84% yield); crystallization (hexanes−CH_2Cl_2); mp 83−84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (dd, 1H, J = 8.4, 1.2 Hz), 7.85 (dt, 1H, J = 7.5, 1.2 Hz), 7.75 (td, 1H, J = 8.4, 1.5 Hz), 7.62 (dd, 1H, J = 7.5, 1.5 Hz), 6.38 (s, 1H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 189.5, 145.3, 135.0, 132.6, 131.7, 123.0, 124.4, 69.6. HRMS (ESI+): calcd for $C_8H_6Cl_2NO_3$ $[M + H]^+$ 233.9724, found 233.9723.

Dichloroacetylmorpholine (2h).[23] This compound was purified by flash column chromatography using hexanes−EtOAc (95:5) and obtained as a white solid (135 mg, 68% yield); crystallization (hexanes−CH_2Cl_2); mp 64−65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.21 (s, 1H), 3.76−3.72 (m, 6H), 3.67−3.64 (m, 2H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 162.1, 66.5, 66.1, 65.4, 46.9, 43.3. HRMS (ESI+): calcd for $C_6H_{10}Cl_2NO_2$ $[M + H]^+$ 198.0088, found 198.0087.

2-*N*,*N*-Dimethylamino-4-(dichloromethyl)-1,3,5-triazine (2i). This compound was purified by flash column chromatography using hexanes−EtOAc (95:5) and obtained as a pale yellow oil (195 mg, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (s, 1H), 6.37 (s, 1H), 3.24 (d, J = 1.5 Hz, 6H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 172.0, 166.6, 164.3, 70.3, 36.5, 36.3. HRMS (ESI+): calcd for $C_6H_9Cl_2N_4$ $[M + H]^+$ 207.0204, found 207.0203.

Dimethyl 2-(Dichloromethyl)pyrimidine-4,5-dicarboxylate (2j).[26] This compound was purified by flash column chromatography

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using hexanes−EtOAc (95:5) and obtained as a colorless oil (274 mg, 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.37 (s, 1H), 6.81 (s, 1H), 4.05 (s, 3H), 4.00 (s, 3H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 167.4, 164.3, 162.6, 160.3, 159.4, 121.4, 69.6, 53.6, 53.4. HRMS (ESI +): calcd for $C_9H_9Cl_2N_2O_4$ $[M + H]^+$ 278.9939, found 278.9945.

4-Chloro-2-(dichloromethyl)pyrimidine (2k). This compound was purified by flash column chromatography with hexanes−EtOAc (95:5) and obtained as a white solid (174 mg, 88% yield); crystallization (hexanes−CH_2Cl_2); mp 66−68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.74 (d, 1H, J = 5.4 Hz), 7.40 (d, 1H, J = 5.4 Hz), 6.72 (s, 1H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 165.9, 162.1, 159.0, 121.8, 69.8. HRMS (ESI+): calcd for $C_5H_4Cl_3N_2$ $[M + H]^+$ 196.9440, found 196.9437.

4-Chloro-2-(dichloromethyl)-5-methylpyrimidine (2l). This compound was purified by flash column chromatography using hexanes−EtOAc (98:2) and obtained as a colorless oil (148 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, J = 0.5 Hz, 1H), 6.71 (s, 1H), 2.42 (d, J = 0.5 Hz, 3H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 163.5, 161.7, 158.8, 130.7, 69.8, 16.3. HRMS (ESI+): calcd for $C_6H_6Cl_3N_2$ $[M + H]^+$ 210.9596, found 210.9596.

4-Chloro-2-(dichloromethyl)-5-phenylpyrimidine (2m). This compound was purified by flash column chromatography using hexanes−EtOAc (98:2) and obtained as a white solid (225 mg, 82% yield); crystallization (hexanes−CH_2Cl_2); mp 82−84 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.53−7.51 (m, 3H), 7.50−7.47 (m, 2H), 6.77 (s, 1H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 164.1, 159.9, 159.0, 134.6, 132.7, 129.5, 129.2, 128.8, 69.7. HRMS (ESI+): calcd for $C_{11}H_7Cl_3N_2$ $[M + H]^+$ 272.9753, found 272.9764.

4,5-Dichloro-6-methyl-2-(dichloromethyl)pyrimidine (2n). This compound was purified by flash column chromatography using hexanes−EtOAc (99:1) and obtained as a white solid (172 mg, 70% yield); crystallization (hexanes−CH_2Cl_2); mp 52−53 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65 (s, 1H), 2.72 (s, 3H). ^{13}C {1H} NMR (125 MHz, $CDCl_3$): δ 168.0, 161.8, 159.2, 129.2, 69.4, 23.3. HRMS (ESI+): calcd for $C_6H_5Cl_4N_2$ $[M + H]^+$ 244.9206, found 244.9212.

5-Bromo-4-chloro-2-(dichloromethyl)pyrimidine (2o). This compound was purified by flash column chromatography using hexanes−EtOAc (96:4) and obtained as a colorless oil (224 mg, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (s, 1H), 6.69 (s, 1H). ^{13}C {1H} NMR (75 MHz, $CDCl_3$): δ 163.9, 161.1, 160.6, 120.5, 69.2. HRMS (ESI+): calcd for $C_5H_3BrCl_3N_2$ $[M + H]^+$ 276.8524, found 276.8524.

2-(Dichloromethyl)quinazoline (2p). This compound was purified by flash column chromatography with hexanes−EtOAc (95:5) and obtained as a white solid (181 mg, 85% yield); crystallization (hexanes−CH_2Cl_2); mp 124−125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (s, 1H), 8.10−7.99 (m, 3H), 7.77- 7.75 (m, 1H), 6.95 (s, 1H). ^{13}C {1H} NMR (125 MHz, $CDCl_3$): δ 162.0, 161.3, 149.6, 135.0, 129.1, 128.7, 127.2, 124.1, 71.4. HRMS (ESI+): calcd for $C_9H_7Cl_2N_2$ $[M + H]^+$ 212.9986, found 212.9983.

2-(Dichloromethyl)-4-methylquinazoline (2q). This compound was purified by flash column chromatography with hexanes−EtOAc (95:5) and obtained as a white solid (182 mg, 80% yield); crystallization (hexanes−CH_2Cl_2); mp 138−141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, 1H, J = 8.1 Hz), 8.07 (d, 1H, J = 8.4 Hz), 7.97−7.90 (m, 1H), 7.73−7.68 (m, 1H), 6.89 (s, 1H), 3.03 (s, 3H). ^{13}C {1H} NMR (125 MHz, $CDCl_3$): δ 170.5, 160.5, 149.2, 134.3, 129.3, 128.6, 125.1, 123.6, 71.7, 21.9. HRMS (ESI+): calcd for $C_{10}H_9Cl_2N_2$ $[M + H]^+$ 227.0142, found 227.0142.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02044.

Copies of ^{1}H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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