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Synthesis of Aryl-Substituted Pyrimidines by Site-Selective Suzuki–Miyura Cross-Coupling Reactions of 2,4,5,6-Tetrachloropyrimidine

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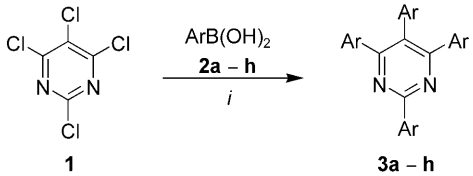
Abstract: Suzuki–Miyaura reactions of 2,4,5,6-tetrachloropyrimidine allow a convenient synthesis of mono-, di-, tri- and tetraarylpyrimidines which are not readily available by other methods. All reactions proceed with excellent site-selectivity.

Keywords: nitrogen heterocycles; palladium; regioselectivity; Suzuki–Miyaura reaction

Pyrimidines are of considerable pharmacological importance and occur in many synthetic drugs and natural products.[1,2] Pyrimidines represent a core structure in analgesic, antihypertensive, antipyretic, and anti-inflammatory drugs. They also play a role as pesticides, herbicides, and plant growth regulators.[3] L-Lathyrine has been reported to show pollen growth inhibition, antitumor and hypoglycemic activity.[4] Most of the syntheses known to date for the synthesis of substituted pyrimidines rely on the application of a building block approach. Pinner developed the first synthesis of pyrimidines based on the cyclocondensation of amidines with 1,3-diketones.[5] A number of related cyclocondensations have been reported.[6,7] Müller and co-workers reported an interesting palladium-catalyzed 3-component reaction for the synthesis of amidines.[8] An alternative approach to substituted pyrimidines is based on the functionalization of appropriate pyrimidine derivatives. For example, nucleophilic aromatic substitution reactions of Grignard reagents with pyrimidines have been reported.[9,10] Monohalogenated pyrimidines have been successfully used in Negishi[11] and Suzuki[12] coupling reactions. Polyhalogenated pyrimidines represent interesting substrates for multiple coupling reactions. Nucleophilic aromatic substitution reactions of 2,4,6-trichloropyrimidine with various nucleophiles have been studied.[10,13] Schomaker and Delia reported site-selective Suzuki–Miyaura reactions of 2,4,6-trichloropyrimidine.[14] 2,4,5,6-Tetrachloropyrimidine represents an interesting substrate because all four carbon atoms are halogenated. Nucleophilic substitution reactions of the latter are known and allow the functionalization of carbon atoms C-2, C-4 and C-6 while carbon atom C-5 remains unattacked.[15] Herein, we report our results related to Suzuki–Miyaura reactions of 2,4,5,6-tetrachloropyrimidine.[16] The reactions reported herein provide a convenient access to a variety of aryl-substituted pyrimidines which are not readily available by other methods.

The Suzuki–Miyaura reaction of commercially available 2,4,5,6-tetrachloropyrimidine (**1**) with arylboronic acids **2a–h** (4.4 equiv.) afforded the 2,4,5,6-tetraarylpyrimidines **3a–h** (Scheme 1, Table 1). This type of molecule has been previously prepared by cyclocondensation reactions, however, their synthesis requires several steps.[17] Products **3a–g** were isolated in good to excellent yields (both for electron-rich and electron-poor arylboronic acids). The yield of **3h** was rather low and a considerable amount of the 2,4,6-triaryl-5-chloropyrimidine was isolated (presumably due to steric reasons). The reaction was thoroughly optimized for derivatives **3a–d** (Table 2). The best yields were obtained when $Pd(PPh_3)_2Cl_2$ (5 mol%) was used as the catalyst (dioxane, 100 °C, 8 h) (entry 1). Excel-



Scheme 1. Synthesis of **3a–h**. *Conditions: i*, **2a–h** (4.4 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%), K_2CO_3 (H_2O, 2 M), dioxane, 100 °C, 8 h; for **3a–g**: 79–98% yields.

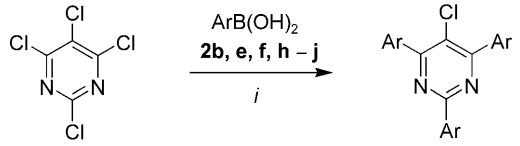
Table 1. Synthesis of **3a–h**.

2, **3**	Ar	Yield [%] of **3**[a]
a	Ph	98
b	4-MeC_6H_4	95
c	4-EtC_6H_4	93
d	4-$(MeO)C_6H_4$	91
e	4-FC_6H_4	89
f	2-$(MeO)C_6H_4$	82
g	3,5-$Me_2C_6H_3$	79
h	3-PhC_6H_4	25 + 43[b]

[a] Yields of isolated products.
[b] Besides **3h**, 2,4,6-triaryl-5-chloropyrimidine **4d** was isolated in 43% yield.

lent yields were obtained when an aqueous solution of K_2CO_3 (2 M) (entry 1) or when K_3PO_4 were employed as the base (entry 5). The amount of catalyst could be reduced to 2.5 mol% without decrease in yield (entry 4). However, complex product mixtures were formed when the amount of the catalyst was reduced further (entries 2 and 3). The yields dropped when $Pd(PPh_3)_4$ or $Pd(OAc)_2$ (5 mol%) in the presence of XPhos or SPhos[18] were employed (entries 8–10). The use of $Pd(OAc)_2$ (5 mol%) in the presence of P(*t*-Bu)$_3$·HBF_4 (entry 11) or of $Pd(OAc)_2$ (5 mol%) in the presence of triethanolamine and 2 M K_2CO_3 (entry 12) gave unsatisfactory results. The employment of $Pd(OAc)_2$ (5 mol%), P(*n*-Bu)$_3$ gave good yields for **3b** and **3d** (entry 13). The amount of $Pd(OAc)_2$ could be reduced to 2.5 mol% when $P(OEt)_2Ph$ was used as the ligand (entry 14). In conclusion, the conditions given in entries 4 and 14 of Table 2 allowed us to prepare the products in excellent yield using only 2.5 mol% of the palladium catalyst.

The Suzuki–Miyaura reaction of **1** with arylboronic acids **2b**, **e**, **f**, **h–j** (3.0 equiv.) gave the 2,4,6-triaryl-5-chloropyrimidines **4a–f** (Scheme 2, Table 3). Good yields were obtained both for electron-rich and elec-



1 **4a – f**

Scheme 2. Synthesis of **4a–f**. *Conditions: i*, **2b**, **e**, **f**, **h–j** (3.0 equiv.), $Pd(PPh_3)_2Cl_2$ (2.0 to 5.0 mol%), K_2CO_3 (H_2O, 2 M), dioxane, 80 °C, 5 h; 80–85% yields.

Table 3. Synthesis of 2,4,6-triaryl-5-chloropyrimidine **4a–f**.

2	**4**	Ar	Yield [%] of **4**[a]
b	**a**	4-MeC_6H_4	83[b]
e	**b**	4-FC_6H_4	83[c]
f	**c**	2-$(MeO)C_6H_4$	81[c]
h	**d**	3-PhC_6H_4	80[c]
i	**e**	3-$CF_3C_6H_4$	82[b]
j	**f**	4-$CF_3C_6H_4$	85[b]

[a] Yields of isolated products.
[b] 2.0 mol% of catalyst were used.
[c] 5.0 mol% of catalyst were used.

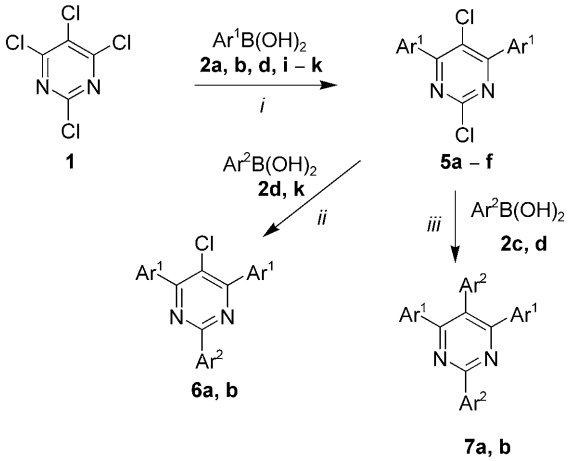
Table 2. Optimization of the reaction conditions for the synthesis of **3a–d**.

Entry	Conditions	Yield [%] of **3a**[a]	Yield [%] of **3b**[a]	Yield [%] of **3c**[a]	Yield [%] of **3d**[a]
1	$Pd(PPh_3)_2Cl_2$ (5 mol%), 2 M K_2CO_3	98	95	93	91
2	$Pd(PPh_3)_2Cl_2$ (1 mol%), 2 M K_2CO_3	_[b]	_[b]	_[b]	_[b]
3	$Pd(PPh_3)_2Cl_2$ (2 mol%), 2 M K_2CO_3	_[c]	_[c]	_[c]	_[c]
4	**$Pd(PPh_3)_2Cl_2$ (2.5 mol%), 2 M K_2CO_3**	**97**	**94**	**94**	**91**
5	$Pd(PPh_3)_2Cl_2$ (5 mol%), K_3PO_4	95	94	93	89
6	$Pd(PPh_3)_4$ (5 mol%), aq. K_2CO_3 (2 M)	81	80	83	77
7	$Pd(PPh_3)_4$ (5 mol%), K_3PO_4	83	80	82	75
8	$Pd(OAc)_2$ (5 mol%), XPhos (10 mol%), 2 M K_2CO_3	71	69	59	58
9	$Pd(OAc)_2$ (5 mol%), XPhos (10 mol%), K_3PO_4	71	65	55	59
10	$Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), 2 M K_2CO_3	48	43	33	50
11	$Pd(OAc)_2$ (5 mol%), P(*t*-Bu)$_3$·HBF_4 (10 mol%), K_3PO_4	_[e]	38	_[e]	32
12	$Pd(OAc)_2$(5 mol%), triethanolamine, 2 M K_2CO_3	_[e]	_[d]	_[e]	_[d]
13	$Pd(OAc)_2$ (5 mol%), P(*n*-Bu)$_3$ (10 mol%), 2 M K_2CO_3	_[e]	70	_[e]	87
14	**$Pd(OAc)_2$ (2.5 mol%), $P(OEt)_2Ph$ (5 mol%), 2 M K_2CO_3**	**93**	**92**	**90**	**96**

[a] Yields of isolated products; all reactions were carried out in dioxane (100 °C, 8 h).
[b] Formation of a complex mixture of mono-, di-, tri-, and tetraarylpyrimidines and of starting material.
[c] Approximately 80% conversion after 12 h (estimated by TLC).
[d] Decomposition.
[e] Experiment was not carried out.

tron-poor arylboronic acids. During the optimization, it proved to be important to use exactly 3.0 equiv. of the boronic acid and to carry out the reaction at 80 °C (5 h) instead of 100 °C (8 h) to avoid the formation of tetraarylpyrimidines. To a small extent, reduction of the unreacted chloride group and formation of tetraarylpyrimidines were observed as side reactions. All products were prepared using $Pd(PPh_3)_2Cl_2$. Initially, 5.0 mol% of the catalyst was used (**4b–d**). Later, we have found that the use of 2.0 mol% of catalyst is sufficient to achieve equally good yields (products **4a**, **e**, **f**).

The Suzuki–Miyaura reaction of **1** with arylboronic acids **2a**, **b**, **d**, **i–k** (2.0 equiv.) afforded the 4,6-diaryl-2,5-dichloropyrimidines **5a–f** (Scheme 3, Table 4). The stoichiometry (employment of exactly 2.0 equiv. of the arylboronic acid), the temperature (not more than 70 °C), and the reaction time (5 h) again played an important role to avoid multiple-coupling reactions.



Scheme 3. Synthesis of **5a–f**, **6a**, **b** and **7a**, **b**. *Conditions: i*, **2a**, **b**, **d**, **i–k** (2.0 equiv.), $Pd(PPh_3)_2Cl_2$ (1.25 to 3.0 mol%), K_2CO_3 (H_2O, 2 M), dioxane, 70 °C, 5 h; *ii*, **2d**, **k** (1.0 equiv.), $Pd(PPh_3)_2Cl_2$ (3 mol%), K_2CO_3 (H_2O, 2 M), dioxane, 80 °C, 5 h; *iii*, **2c**, **d** (2.0 equiv.), $Pd(PPh_3)_2Cl_2$ (1.25 to 3 mol%), K_2CO_3 (H_2O, 2 M), dioxane, 100 °C, 5 h; for **5a–f**, **6a**, **b**, and **7a**, **b**: 79–97% yields.

Table 4. Synthesis of 2,4,6-triaryl-5-chloropyrimidine **5a–f**.

2	5	Ar^1	Yield [%] of 5[a]
a	**a**	Ph	97[b]
b	**b**	4-MeC_6H_4	85[b]
d	**c**	4-(MeO)C_6H_4	93[b]
i	**d**	3-$CF_3C_6H_4$	90[c]
j	**e**	4-$CF_3C_6H_4$	88[c]
k	**f**	4-ClC_6H_4	84[c]

[a] Yields of isolated products.
[b] 3.0 mol% of catalyst were used.
[c] 1.25 mol% of catalyst were used.

Products **5a–c** were prepared using 3 mol% of $Pd(PPh_3)_2Cl_2$. Later, we have found that the use of only 1.25 mol% proved to be sufficient (products **5d–f**). The reaction of **5a** with arylboronic acids **2d**, **k** (1.0 equiv.) (80 °C, 5 h) gave the 2,4,6-triaryl-5-chloropyrimidines **6a**, **b** (Scheme 3, Table 5). The reaction of

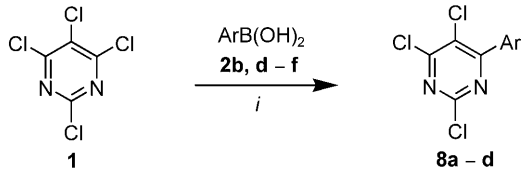
Table 5. Synthesis of **6a**, **b** and **7a**, **b**.

2	5	6, 7	Ar^1	Ar^2	Yield [%] of 6, 7[a]
k	**a**	**6a**	Ph	4-ClC_6H_4	90[b]
d	**a**	**6b**	Ph	4-(MeO)C_6H_4	86[b]
d	**a**	**7a**	Ph	4-(MeO)C_6H_4	79[b]
c	**d**	**7b**	3-$CF_3C_6H_4$	4-EtC_6H_4	89[c]

[a] Yields of isolated products.
[b] 3.0 mol% of catalyst were used.
[c] 1.25 mol% of catalyst were used.

5a, **d** with 2.0 instead of 1.0 equiv. of arylboronic acid **2c**, **d** (100 °C, 5 h) afforded the 2,4,5,6-tetraarylpyrimidines **7a**, **b**. Reduction of the unreacted chloride group and multiple coupling were again observed as side reactions, albeit, to a small extent.

The Suzuki–Miyaura reaction of **1** with arylboronic acids **2b**, **d–f** (1.0 equiv.) gave the 6-aryl-2,4,5-trichloropyrimidines **8a–d** (Scheme 4, Table 6). The stoichiometry (employment of not more than 1.0 equiv. of the arylboronic acid), the temperature, and the reaction time again played an important role during the optimization. It proved to be important to carry out the reaction at 60 °C for only 2 h to avoid multiple-coupling reactions. All products were again



Scheme 4. Synthesis of **8a–d**. *Conditions: i*, **2b**, **d–f** (1.0 equiv.), $Pd(PPh_3)_2Cl_2$ (1.0 to 3.0 mol%), K_2CO_3 (H_2O, 2 M), dioxane, 60 °C, 2 h; 87–97% yields.

Table 6. Synthesis of 6-aryl-2,4,5-trichloropyrimidines **8a–d**.

2	8	Ar	Yield [%] of 8[a]
b	**a**	4-MeC_6H_4	87[b]
d	**b**	4-(MeO)C_6H_4	95[c]
e	**c**	4-FC_6H_4	93[c]
f	**d**	2-(MeO)C_6H_4	97[c]

[a] Yields of isolated products.
[b] 1.0 mol% of catalyst was used.
[c] 3.0 mol% of catalyst were used.

prepared using $Pd(PPh_3)_2Cl_2$ as the catalyst. Although 3.0 mol% of the catalyst was used in most cases (products **8b–d**), the employment of only 1.0 mol% of catalyst proved to be possible to achieve equally good yields (product **8a**).

The structures of all products were confirmed by 2D NMR methods (NOESY, HMBC) or by X-ray crystal structure analyses.

In conclusion, we have reported a convenient synthesis of mono-, di-, tri- and tetraarylpyrimidines by Suzuki–Miyaura reactions of 2,4,5,6-tetrachloropyrimidine. The products reported herein are not readily available by other methods. All reactions proceed with excellent site-selectivity. We are currently studying the synthesis of unsymmetrical tetraarylpyrimidines based on reactions of 6-aryl-2,4,5-trichloropyrimidines **8** and of pyrimidines **4** and **6**.

Experimental Section

General Procedure for Suzuki–Miyaura Reactions

The reaction was carried out in a pressure tube. To a dioxane suspension (3–5 mL) of the chlorinated pyrimidine, $Pd(PPh_3)_2Cl_2$ (1–5 mol%) and of the arylboronic acid was added an aqueous solution of K_2CO_3 (2 M, 1–2 mL). The mixture was heated at the indicated temperature (60–100 °C) under an argon atmosphere for the indicated period of time (2–8 h). The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (silica gel, EtOAc/heptanes).

2,4,5,6-Tetraphenylpyrimidine **(3a):** Starting with **1** (87 mg, 0.40 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg, 5 mol%), dioxane (3 mL), K_2CO_3 (H_2O, 2 M, 1 mL) and phenylboronic acid (215 mg, 1.76 mmol), reaction temperature: 100 °C for 8 h. **3a** was isolated as a white solid; yield: 150 mg (98%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.88–6.92 (m, 2H, ArH), 7.06–7.20 (m, 8H, ArH), 7.31–7.44 (m, 8H, ArH), 8.55–8.59 (m, 2H, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 127.2 (C), 127.3, 127.8, 128.3, 128.4, 128.5, 128.6, 130.0, 130.6, 131.1 (CH), 136.6, 137.8, 138.8, 162.9, 165.4 (C); IR (KBr): $\tilde{\nu}$ = 3059, 2916, 2852 (w), 1536, 1488 (s), 1442, 1370, 1298 (m), 1246 (s), 1194, 1179, 1090, 1079, 1024, 1000 (m), 965, 929, 912 (w), 866, 800, 750, 729, (m), 688 (s), 620, 614, 605, 592 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 383 ([M]$^+$, 100), 331 (1), 305 (4), 280 (5), 178 (9); HR-MS (EI, 70 eV): *m/z* = 384.16299, calcd. for $C_{22}H_{20}N_2$ [M]$^+$: 384.16265.

2,5-Dichloro-4,6-bis(4-methoxyphenyl)pyrimidine **(5c):** Starting with **1** (217 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (21 mg, 3 mol%), dioxane (5 mL), 2 M K_2CO_3 (2 mL) and 4-methoxyphenylboronic acid (304 mg, 2.0 mmol), reaction temperature: 70 °C for 5 h. **5c** was isolated as a white solid; yield: 334 mg (93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 6H, OCH_3), 6.95 (d, 4H, *J* = 9.1 Hz, ArH), 7.85 (d, 4H, *J* = 9.1 Hz, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 113.6 (CH), 124.6, 127.9 (C), 131.5 (CH), 158.0, 161.6, 166.5 (C); IR (KBr): $\tilde{\nu}$ = 2878, 2966, 2935, 2826 (w), 1611, 1523, 1513, 1511, 1483, 1468, 1433, 1333, 1325, 1321, 1274 (m), 1255 (s), 1178, 1117, 1097, 1038, 1018 (m), 961 (w), 866 (m), 822, 820, 806, 773, 766 (s), 728 (m), 692, 667, 632 (w), 614, 578, 562 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 360 ([M]$^+$, 100), 325 (33), 253 (11), 252 (4), 236 (9), 132 (10); HR-MS (EI, 70 eV): *m/z* = 360.0431, calcd. for $C_{18}H_{14}Cl_2N_2O_2$ [M]$^+$: 360.04323.

5-Chloro-2-(4-methoxyphenyl)-4,6-diphenylpyrimidine **(6b):** Starting with **1** (75 mg, 0.25 mmol), $Pd(PPh_3)_2Cl_2$ (6 mg, 3 mol%), dioxane (3 mL), 2 M K_2CO_3 (1 mL) and 4-methoxyphenylboronic acid (38 mg, 0.25 mmol), reaction temperature: 80 °C for 5 h. **6b** was isolated as a white solid; yield: 80 mg (86%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.81 (s, 3H, OCH_3), 6.90 (d, 2H, *J* = 9.0 Hz, ArH), 7.43–7.50 (m, 6H, ArH), 7.82–7.87 (m, 4H, ArH), 8.44 (d, 2H, *J* = 9.0 Hz, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 113.8 (CH), 123 (C), 128.1 (CH), 129.5 (C), 129.7 (CH), 129.8 (CH), 130.2 (CH), 137.3, 162.0, 164.5 (2C); IR (KBr): $\tilde{\nu}$ = 3059, 3028, 3006, 2954, 2931, 2835 (w), 1608, 1560, 1534 (m), 1504, 1490 (s), 1468, 1444, 1423, 1385 (m), 1361 (s), 1302 (m), 1250 (s), 1174, 1106, 1075, 1058, 1037, 1030, 1002 (m), 980, 969, 958, 912, 864 (w), 838, 797, 787, 771 (m), 757 (s), 729 (m), 687 (s), 632, 615, 540 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 372 ([M]$^+$, 100), 357 (3), 337 (4), 204 (12), 136 (22); HR-MS (EI, 70 eV): *m/z* = 372.10278 calcd. for $C_{23}H_{17}ClN_2O$ [M]$^+$: 372.10294.

2,4,5-Trichloro-6-(4-methoxyphenyl)pyrimidine **(8a):** Starting with **1** (217 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (21 mg, 3 mol%), dioxane (5 mL), 2 M K_2CO_3 (2 mL) and 4-methoxyphenylboronic acid (152 mg, 1.0 mmol), reaction temperature: 60 °C for 2 h. **8a** was isolated as a white solid; yield: 275 mg (95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3H, OCH_3), 6.94 (d, 2H, *J* = 9.0 Hz, ArH), 7.83 (d, 2H, *J* = 9.0 Hz, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.5 (OCH_3), 113.8 (CH), 126.8 (C), 131.7 (CH), 156.9, 161.4, 162.2, 166.0 (C); IR (KBr): $\tilde{\nu}$ = 2971, 2928, 2836 (w), 1604, 1574, 1530, 1511, 1483, 1458, 1446, 1372, 1325, 1317, 1309, 1284 (m), 1253 (s), 1177, 1116, 1097, 1038, 1025 (m), 962 (w), 867 (m), 832, 820, 807, 774, 766 (s), 729 (m), 691, 668, 634 (w), 615, 579, 569, 537 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 288 ([M]$^+$, 100), 275 (04), 253 (17), 210 (14), 157 (7); HR-MS (EI, 70 eV): *m/z* = 287.96228, calcd. for $C_{11}H_7Cl_3N_2O$ [M]$^+$: 287.96240.

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