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# Novel Synthesis of 2-Chloroquinolines from 2-Vinylanilines in Nitrile Solvent

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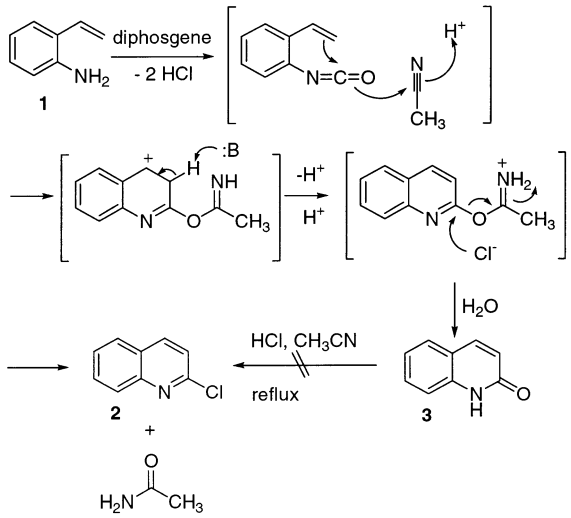
**Abstract:** 2-Vinyl- or heteroaryl-substituted anilines were reacted with diphosgene in acetonitrile solution via a reactive imidoyl moiety to afford the corresponding 2-chloroquinolines. Facile syntheses of nine 2-chloroquinoline derivatives from several anilines and their postulate mechanism is described. The postulate mechanism of 2-chloroquinoline formation via imidoyl moiety as a good leaving group shows that the reaction consists of the following three steps: (1) generation of phenylisocyanate, (2) quinoline ring formation, and (3) chlorination on C2 position of quinoline.

2-Chloroquinolines have been considered key intermediates in the syntheses of a number of quinoline compounds because the chlorine on the C2 position can be easily replaced with nucleophiles such as nitrogen,[1,2] oxygen, or sulfur as well as undergo cross-coupling by transition-metal catalyst.[3−7] 2-Chloroquinolines are usually prepared from 2(1*H*)-quinolinone by using an excessive amount of phosphorus oxychloride under reflux conditions.[2,8] However, it is hazardous and inefficient to remove the excess phosphorus oxychloride residue after the reaction is completed. There are many reports of the synthesis of 2(1*H*)-quinolinones through the reaction of 2-alkenylanilines and phosgene or phenyl isocyanates in the presence of Lewis acids in several organic solvents.[2,9−14] However, 2-chloroquinoline was not obtained under these conditions.

**SCHEME 1**




When the reaction of 2-vinylaniline (**1a**) and diphosgene was carried out in acetonitrile for the purpose of the preparation of 2(1*H*)-quinolinone (**3**), 2-chloroquinoline (**2a**) was obtained instead of 2(1*H*)-quinolinone (**3**). This result makes it possible to eliminate an unnecessary step: the chlorination of 2(1*H*)-quinolinone that needs excess phosphorus oxychloride. In this paper, we report not only a new 2-chloroquinoline synthesis from 2-vinylanilines and diphosgene but also its postulated mechanism involving acetonitrile.

Scheme 1 illustrates the postulated mechanism of a 2-chloroquinoline formation via an imidoyl moiety as a good leaving group. The reaction consists of the following three steps: (1) generation of phenyl isocyanate, (2) quinoline ring formation, and (3) chlorination on C2 position of quinoline.

In the first step, phenyl isocyanate is formed by the reaction of 2-vinylaniline and diphosgene. Acetonitrile is protonated by *in situ* generated hydrochloride to provide protonated acetonitrile. It was reported not only that dry HCl−alkyl cyanide forms imidoyl chloride as a reactive species under Hoesch reaction conditions but also that imidoyl chloride was isolated and identified.[15] Whether the reactive form is imidoyl chloride or protonated acetonitrile, in the second step, the $\pi$-electrons of the olefin attack the partially positive carbon of isocyanate to form a quinoline ring. The generated oxygen anion attacks protonated acetonitrile. This push−pull mechanism including activation by solvent assistance would make it possible to dramatically decrease the activation barrier for quinoline ring formation. Acetimidic acid quinolin-2-yl ester, the secondary intermediate, which has a benzylic cation, is aromatized by deprotonation. At this step, acetimidic acid quinolin-2-yl ester may be protonated on the nitrogen of the imidoyl group. This protonated imidoyl group would be a good leaving group when chloride attacks carbon at the C2 position of

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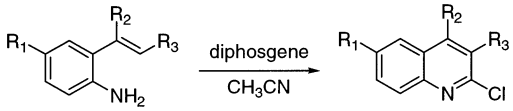
**TABLE 1. 2-Chloroquinoline Formations of 2-Alkenylanilines with Diphosgene in Acetonitrile**[a]




**1a-j** **2a-j**

| product | $R^1$ | $R^2$ | $R^3$ | time (h) | yield (%) |
|---|---|---|---|---|---|
| **2a** | H | H | H | 12 | 75 |
| **2b** | Cl | H | H | 12 | 84 |
| **2c** | $CH_3$ | H | H | 10 | 57 |
| **2d** | $CF_3$ | H | H | 12 | 98 |
| **2e** | $NO_2$ | H | H | 3 | 86 |
| **2f** | $NO_2$ | $CH_3$ | H | 10 | 63 |
| **2g** | $NO_2$ | $-CH_2CH_2CH_2CH_2-$ | | 8 | 78 |
| **2h** | $NO_2$ | $-OCH=CHCH-$ | | 24 | 65 |
| **2i** | $NO_2$ | $-SCH=CHCH-$ | | 24 | 36 |
| **2j** | $NO_2$ | $-CHCH=CHS-$ | | 24 | 48 |

[a] All ring formations were carried out with aniline (1 equiv) and diphosgene (1.5 equiv) in $CH_3CN$ at 130 °C in a tightly capped pressure tube.

quinoline. Thus, this aromatic nucleophilic substitution gives 2-chloroquinoline as a product and acetamide as a byproduct.

Although 0.5 equiv of diphosgene is stoichiometrically required for the quantitative conversion of 2-vinylaniline to product, actually, more than 1.5 equiv of diphosgene is required. Moreover, time-dependent HPLC analysis showed that the second step, quinoline ring formation, is more rapid than the third step, chlorination. In addition, on the basis of TLC monitoring and HPLC data, it was observed that starting molecules bearing electron-withdrawing groups were quickly converted to product comparatively. These observations indicate that the third step in Scheme 1 is likely to be the rate-determining step.

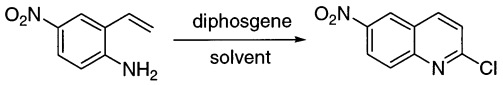
To check whether 2-chloroquinolines could be prepared from 2(1*H*)-quinolinones under the same conditions, 6-nitro-2(1*H*)-quinolinone was reacted in dry HCl acetonitrile solution without diphosgene. However, 2-chloro-6-nitroquinoline was not obtained.

2-Chloroquinoline, four 6-substituted 2-chloroquinolines, two 3,(4)-substituted 2-chloro-6-nitroquinolines, and three five-membered heterocyclic fused 2-chloroquinolines were synthesized from the corresponding 2-vinylanilines and 2-heterocyclic anilines, respectively. All reactions were carried out at 130 °C for 3−24 h in a pressure tube by using 1.5 equiv of diphosgene. Table 1 summarizes the results of the synthesis of 10 2-chloroquinolines by our synthetic method.

Compounds **2b**,**e**,**f**,**h** were obtained by filtering the resulting precipitate, which was formed when water was added to the reaction mixture and then recrystallized with EtOAc/*n*-hexane. In other compounds, the products were isolated by liquid−liquid extraction and flash column chromatography.

To check whether acetonitrile would take part in the reaction as a reagent, first, the reaction was performed in other solvents such as toluene, 1,4-dioxane, carbon tetrachloride, and DMF under the same conditions. However, 2-chloroquinoline was not obtained in all cases. Second, acetamide was detected as a byproduct by using HPLC.[16] Without using nitrile solvent, Künzle and Schmutz reported that 2-chloro-4-phenylquinoline, in only one case, was obtained in 88% yield by treating 1-(2-aminophenyl)-1-phenylethylene in the presence of excess of phosgene in refluxing toluene.[17] It could be explained that the chlorocarbonyoxy group on the C2 position could be formed in the presence of excess of phosgene, and it acts as a good leaving group.

**TABLE 2. 2-Chloroquinoline Formations of 4-Nitro-2-vinylaniline in Various Nitrile Solvents**




| entry | solvent | *T* (°C) | time (h) | yield (%) |
|---|---|---|---|---|
| 1 | acetonitrile | 130 | 3 | 86 |
| 2 | benzonitrile | 150 | 12 | 83 |
| 3 | benzyl cyanide | 150 | 12 | 71 |

We also used other nitrile solvents such as benzonitrile and benzyl cyanide to determine the role of the nitrile group. The mixtures of 4-nitro-2-vinylaniline and 1.5 equiv of diphosgene in benzonitrile or benzyl cyanide were stirred at 150 °C for 12 h in a pressure tube. After the residues of benzonitrile and benzyl cyanide were distilled out, the desired product, 2-chloro-6-nitroquinoline, was obtained by flash column chromatography in 83% and 71% yield, respectively. At this time, benzamide and α-phenylacetamide were generated as byproducts and identified by NMR and MS spectra (Table 2).

Nitrile compounds can be trimerized with various acids, bases, or other catalysts.[18,19] In this reaction, acetonitrile could be trimerized by in situ generated HCl to give 2,4,6-trimethyl-1,3,5-triazine, which was gradually increased with the reaction time. This triazine could be easily removed either by column chromatography or by washing the precipitate with hexane.

The starting molecules used in this paper were prepared by Stille cross-coupling reaction of 2-iodoacetanilides and substituted tributyl(vinyl)tins or tributylstannanylheterocyclics in the presence of 2 mol % $Pd(PPh_3)_4$.

In summary, we have demonstrated a novel synthesis of 2-chloroquinolines from 2-vinylanilines and diphosgene in nitrile solvent. Its postulated mechanism shows that this reaction consists of the following three steps: (1) generation of phenylisocyanate, (2) quinoline ring formation, and (3) chlorination on the C2 position of quinoline. On the basis of time-dependent HPLC analysis and the propensity that starting molecules bearing electron-withdrawing groups were quickly converted to product comparatively, the third step is likely to be a rate-determining step. It is expected that this result can be applied to the synthesis other heterocyclic compounds.

## Experimental Section

**General Procedure for the Preparation of 2-Chloroquinolines 2a−j.** Under $N_2$ atmosphere, to a solution of 2-vinylanilines **1a−j** (0.62 mmol) in 3 mL of $CH_3CN$ (molecular sieve dried) was added diphosgene (0.111 mL, 0.93 mmol) at rt

(16) Analytic conditions: Alltech econosil C-18 (250 mm × 4.6 mm), water/acetonitrile = 60:40, flow rate 0.7 mL/min, 210 nm). Authentic acetamide has a retention time of 7.3 min.

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(white precipitate was formed). The reaction mixture in a tightly capped pressure tube was stirred for 12 h at 130 °C and then cooled to rt. Water was carefully added to the mixture and allowed to stand for 30 min at rt. The resulting precipitate was filtered, washed with water, and dried under suction for 5 h to give 2-chloroquinolines **2a**−**j**.

**2-Chloroquinoline** (**2a**)**:** commercially available; 75% yield as a white solid; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.10 (d, 1H, $J$ = 8.6 Hz), 8.03 (d, 1H, $J$ = 8.8 Hz), 7.82 (d, 1H, $J$ = 7.8 Hz), 7.70−7.78 (m, 1H), 7.52−7.60 (m, 1H), 7.39 (d, 1H, $J$ = 8.6 Hz).

**2,6-Dichloroquinoline** (**2b**)**:** 84% yield as a white solid; mp 164−165 °C (lit.[20] mp 161.5 °C); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.03 (d, 1H, $J$ = 9.0 Hz), 7.96 (d, 1H, $J$ = 9.0 Hz), 7.81 (d, 1H, $J$ = 2.4 Hz), 7.67 (dd, 1H, $J$ = 9.0, 2.4 Hz), 7.41 (d, 1H, $J$ = 8.6 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 151.0, 146.2, 137.8, 132.8, 131.4, 130.1, 127.4, 126.3, 123.3; MS (EI) *m*/*z* (relative intensity) 201 ($M^+$), 199 ($M^+$), 197 ($M^+$, 100), 162, 127, 99, 81, 75.

**2-Chloro-6-methylquinoline** (**2c**)**:** 57% yield as a yellow solid; mp 111−114 °C (lit.[20] mp 113−114 °C); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.00 (d, 1H, $J$ = 8.4 Hz), 7.90 (d, 1H, $J$ = 9.4 Hz), 7.52−7.57 (m, 2H), 7.33 (d, 1H, $J$ = 8.4 Hz), 2.52 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 149.6, 146.3, 138.0, 136.8, 132.6, 128.1, 126.7, 126.3, 122.1, 21.4; MS (EI) *m*/*z* (relative intensity) 179 ($M^+$), 177 ($M^+$, 100), 142, 115, 89, 70.

**2-Chloro-6-trifluoromethylquinoline** (**2d**)**:** 98% yield as a white solid; mp 97−99 °C; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.20 (d, 1H, $J$ = 8.8 Hz), 8.12−8.16 (m, 2H), 7.92 (dd, 1H, $J$ = 8.7, 1.9 Hz), 7.50 (d, 1H, $J$ = 8.4 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 153.0, 148.7, 139.3, 129.7, 128.8 (q, $J$ = 32.6 Hz), 126.2 (q, $J$ = 2.9 Hz), 125.4 (q, $J$ = 4.3 Hz), 123.7, 123.7 (q, $J$ = 270.8 Hz), 121.0; MS (CI) *m*/*z* (relative intensity) 234 ($MH^+$), 232 ($MH^+$, 100), 212, 168; HRMS (CI) *m*/*z* $C_{10}H_6ClF_3N$ ($MH^+$) calcd 232.0116, found 232.0148.

**2-Chloro-6-nitroquinoline** (**2e**)**:** 86% yield as a white solid; mp 236−237 °C (lit.[20] mp 235 °C); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.80 (d, 1H, $J$ = 2.6 Hz), 8.52 (dd, 1H, $J$ = 9.2, 2.6 Hz), 8.30 (d, 1H, $J$ = 8.6 Hz), 8.16 (d, 1H, $J$ = 9.6 Hz), 7.57 (d, 1H, $J$ = 8.8 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 152.6, 148.3, 144.5, 140.8, 128.8, 125.0, 123.9, 123.3, 123.0; MS (EI) *m*/*z* (relative intensity) 210 ($M^+$), 208 ($M^+$), 162, 127 (100). Anal. Calcd for $C_9H_8N_2O_3$: C, 51.92; H, 2.42; N, 13.43. Found: C, 51.99; H, 2.42; N, 13.14.

**2-Chloro-4-methyl-6-nitroquinoline** (**2f**)**:** 65% yield as a white solid; mp 214−215 °C; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.92 (d, 1H, $J$ = 2.6 Hz), 8.49 (dd, 1H, $J$ = 9.2, 2.6 Hz), 8.13 (d, 1H, $J$ = 9.2 Hz), 7.40 (d, 1H, $J$ = 0.8 Hz), 2.79 (d, 3H, $J$ = 1.2 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 154.4, 150.0, 149.6, 145.6, 130.9, 126.2, 124.5, 123.8, 120.7, 18.6; MS (EI) *m*/*z* (relative intensity) 224 ($M^+$), 222 ($M^+$), 192, 164, 140 (100), 114, 89, 75; HRMS (CI) *m*/*z* $C_{10}H_8ClN_2O_2$ ($MH^+$) calcd 223.0271, found 223.0275.

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**6-Chloro-2-nitro-7,8,9,10-tetrahydrophenanthridine** (**2g**)**:** 63% yield as a white solid; mp 185−186 °C; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.83 (d, 1H, $J$ = 2.6 Hz), 8.37 (dd, 1H, $J$ = 9.2, 2.6 Hz), 8.02 (d, 1H, $J$ = 9.2 Hz), 3.17 (t, 2H, $J$ = 5.2 Hz), 2.90 (t, 2H, $J$ = 4.8 Hz), 1.96 (q, 4H, $J$ = 2.9 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 156.3, 147.7, 146.9, 145.5, 131.3, 130.5, 126.2, 122.6, 119.7, 27.4, 25.9, 21.9, 21.4; MS (EI) *m*/*z* (relative intensity) 264 ($M^+$), 262 ($M^+$, 100), 234, 180, 152, 76; HRMS (CI) *m*/*z* $C_{13}H_{12}ClN_2O_2$ ($MH^+$) calcd 263.0585, found 263.0588.

**4-Chloro-8-nitrofuro[3,2-*c*]quinoline** (**2h**)**:** 78% yield as a white solid; mp 208−209 °C; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 9.19 (d, 1H, $J$ = 2.6 Hz), 8.50 (dd, 1H, $J$ = 9.4, 2.6 Hz), 8.26 (d, 1H, $J$ = 9.6 Hz), 7.94 (d, 1H, $J$ = 2.4 Hz), 7.11 (d, 1H, $J$ = 2.4 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 156.3, 148.3, 146.9, 146.6, 145.7, 130.6, 122.7, 121.4, 117.2, 115.9, 106.7; MS (EI) *m*/*z* (relative intensity) 250 ($M^+$), 248 ($M^+$, 100), 202, 190, 174, 139, 88. Anal. Calcd for $C_{11}H_5ClN_2O_3$: C, 53.14; H, 2.03; N, 11.27. Found: C, 53.43; H, 1.97; N, 11.94.

**4-Chloro-8-nitrothieno[3,2-*c*]quinoline** (**2i**)**:** 36% yield as a white solid; mp 253−254 °C; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 9.00 (d, 1H, $J$ = 2.4 Hz), 8.48 (dd, 1H, $J$ = 9.0, 2.2 Hz), 8.25 (d, 1H, $J$ = 9.2 Hz), 7.76 (s, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 149.5, 147.3, 146.1, 133.5, 131.1, 128.4, 124.7, 123.1, 122.8, 119.7, 115.9; MS (ESI) *m*/*z* (relative intensity) 267 ($MH^+$), 265 ($MH^+$, 100), 250, 235, 216, 214, 204. Anal. Calcd for $C_{11}H_5ClN_2O_2S$: C, 49.91; H, 1.90; N, 10.58; S, 12.11. Found: C, 49.93; H, 1.82; N, 10.92; S, 12.53.

**4-Chloro-8-nitrothieno[2,3-*c*]quinoline** (**2j**)**:** 48% yield as a pale yellow solid; mp 288−289 °C; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 9.19 (d, 1H, $J$ = 2.2 Hz), 8.52 (dd, 1H, $J$ = 9.2 Hz), 8.28 (d, 1H, $J$ = 9.0 Hz), 8.12 (d, 1H, $J$ = 5.6 Hz), 8.07 (d, 1H, $J$ = 5.4 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 173.2, 172.8, 147.4, 144.3, 134.8, 130.8, 130.7, 128.9, 123.1, 122.6, 120.1; MS (ESI) *m*/*z* (relative intensity) 267 ($MH^+$), 265 ($MH^+$), 225, 204 (100); HRMS (CI) *m*/*z* $C_{11}H_6ClN_2O_2S$ ($MH^+$) calcd 264.9820, found 264.9845.

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**Supporting Information Available:** Characterization information of **1a**−**j** and time courses of percentage of conversions of 4-nitro-2-vinylaniline (**1e**) depended on the equiv of diphosgene and $^1$H and $^{13}$C NMR spectra of **2a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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