# Rapid and Effective Reaction of 2-Methylpyridin-N-oxides with Triphosgene via a [3,3]-Sigmatropic Rearrangement: Mechanism and Applications

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**ABSTRACT:** A facile and effective synthesis of 2-chloromethylpyridines was developed by a one-pot reaction of 2-alkylpyridin-N-oxides and triphosgene at room temperature. As starting materials, N-oxides of 2-alkylpyridine derivatives, including 2-alkylpyridines, 2-methyl quinolines, and phenanthroline, can react rapidly with triphosgene in the presence of triethylamine, affording 2-chloromethylpyridines in good to excellent yields (52–95%). Using the 2-methylquinoline substrate for the mechanistic study, it has been well demonstrated that the chlorination reaction undergoes a [3,3]-sigmatropic rearrangement, which can be observed as a reversible process by monitoring the intermediates. Moreover, the chlorination reaction can be used to construct a rapid and sensitive fluorescent probe for the detection of phosgene.

# INTRODUCTION

Chloromethylpyridines are an important class of compounds in the preparation of drugs, dyes, and pesticides.<sup>1</sup> 2-Chloromethylpyridine was directly chlorinated from  $\alpha$ -picoline but the yields were low due to the formation of a large number of dichloro- and trichloro-methylated pyridines.<sup>2</sup> 2-Chloromethylpyridine was prepared from 2-methylpyridine-N-oxides by various chlorinating agents, phosphoryl chloride,<sup>3</sup> thionyl dichloride,<sup>4</sup> trichloroacetyl chloride,<sup>5</sup> benzene sulfonyl chloride,<sup>6</sup> or *p*-toluenesulfonyl chloride,<sup>7</sup> shown in Scheme 1. In these reactions, the yields of trichloroacetyl chloride ( $\sim$ 70%), phosphoryl chloride (90%), and sulfonyl chloride (90%) are acceptable or very high, but there are waste disposal problems associated with organochlorinated agents and/or waste heat energy (for a high reaction temperature). Moreover, the chlorinating agents, phosphoryl chloride, trichloroacetyl chloride, and sulfonyl chlorides, generate inorganic salts, which have environmental and treatment problems.

In the presence of a base, triethylamine (TEA), for utilizing phosphoryl chloride, a highly effective conversion (88%) of 2-picoline-*N*-oxide to 2-chloromethylpyridine was achieved.<sup>3b</sup> In the same work, a low yield (35%) was obtained from 2-

picoline-*N*-oxide to 2-chloromethylpyridine using phosgene in the presence of TEA.<sup>3b</sup> In another work, three 2chloromethylpyridines were produced in high yields (72– 92%) from *N*-oxides of three  $\alpha$ -picolines with diphosgene or triphosgene in the presence of a tertiary amine at very low temperatures -20 or -40 °C.<sup>8</sup> In the two papers, however, there is no mention of the reaction mechanism of  $\alpha$ -picoline-*N*-oxides with phosgene and its substitutes, diphosgene (trichloromethyl chloroformate, TCF) and triphosgene (bis-(trichloromethyl)carbonate, BTC).

In this work, we have developed a one-pot synthesis of 2chloromethylpyridines from *N*-oxides of 2-alkylpyridines with BTC in the presence of TEA. The reactions were carried out at room temperature for a very short time, generating only HCl and  $CO_2$  as byproducts. The mechanism has been demon-

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Scheme 1. Synthesis of 2-Chloromethylpyridines from 2-Picoline N-Oxides in Previous Papers<sup>3b,6b,7</sup> and This Work Traditional methods



0.5 ea. triphosgene TFA rt 10 min ò 52-95%

strated by tracking reaction processes and detecting intermediates. Furthermore, another application of this reaction has been exploited for the detection of highly toxic phosgene gas with a 2-methylquinoline N-oxide as a fluorescent probe.

# RESULTS AND DISCUSSION

Synthesis of 2-Chloromethylpyridines from 2-Methylpyridine N-Oxides with BTC. The N-oxide derivatives of

Table 1. Substrate Scope and the Products with Yields<sup>a</sup>

2-alkylpyridine are generally prepared by the reaction of a 2alkylpyridine with 3-chloroperbenzoic acid (*m*-CPBA) at room temperature for 12 h. Various 2-alkylpyridines were prepared by routine methods or literature methods. Their synthesis

routes are described in Supporting information (SI). Since BTC can decompose into phosgene in the presence of a tertiary amine such as TEA, the reaction of 2-methylpyridine N-oxide with BTC in the presence of TEA can be regarded as the reaction with phosgene. Optimization of the conditions was achieved by performing the reaction of 2-methylquinoline N-oxide in seven solvents at room temperature, including the use of different dosages of BTC and TEA (Table S1). In seven solvents, the highest isolated yield of 57% was obtained in dichloromethane (DCM), and the second highest yield (47%) from acetonitrile. For the dosages of BTC and TEA, the reaction with 0.5 equiv of BTC and 5 equiv of TEA afforded the highest yield of 68%. The reaction conditions were used in the next synthesis.

According to the optimized conditions, that is, 0.5 equiv of BTC and 5 equiv of TEA in DCM, we proceeded with the identification of the substrate scope, shown in Table 1. The substrates include 18 N-oxides of various 2-methylpyridine derivatives covering 2-alkylpyridines (2a-e), 7-substituted 2methyl quinolines (2f-h), 6-amino-substituted 2-methyl quinolines (2i-q), and the 2-methyl phenanthroline (2r), prepared according to the literature,<sup>9</sup> and the details are provided as the SI. 2-Chlorinated methyl products 3 were obtained from the reactions of the substrates with BTC/TEA



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<sup>a</sup>Yields determined by high-performance liquid chromatography (HPLC), and isolated yields in brackets.

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at room temperature for 10 min in good to excellent yields (52–95%) (Table 1).

Taking **3r** as an example, in another four-step procedure,<sup>10</sup> the *N*-oxide **2r** was obtained with **1r** as the starting material, and **3r** was prepared by the rearrangement of **2r** with acetic anhydride (90%), hydrolysis (86%), and treatment with PCl<sub>3</sub> (72%), and the total yield of the last three steps was 56%. In our synthesis, a one-pot reaction of **2r** for 10 min at room temperature can afford **3r** in 65% yield. In addition, although incompletely alkylated amino for **2k**, **2l**, and **2q** could react with BTC, their target products were still obtained in good yields (81, 52, and 75%). The results show a good substrate compatibility for the reaction of 2-alkylpyridine *N*-oxides with BTC/TEA under mild conditions.

**Reaction Mechanism.** As the conversion of 2g to 3g is easy to be detected by UV/vis absorption spectroscopy and fluorescence spectroscopy, 2g was selected as a representative for the mechanism study of the reactions of the *N*-oxides with phosgene or its substitutes.

First, the photophysical properties of 2g and 3g were investigated by measuring their UV/vis absorption and fluorescence spectra in seven solvents (Figure S1). In seven solvents, the fluorescence response of 2g toward triphosgene in the presence of TEA is the largest in acetonitrile (CH<sub>3</sub>CN). This should be attributed to the low background fluorescence of 2g, the possible efficient conversion from 2g to 3g, and the high fluorescence efficiency of 3g in acetonitrile. The *N*-oxide 2g is nonfluorescent, and 3g exhibits strong fluorescence with a peak at 397 nm in acetonitrile, and its fluorescence quantum yield ( $\Phi_f$ ) was measured to be 0.1 with quinine sulfate ( $\Phi_f = 0.546^{11}$  in 1 N H<sub>2</sub>SO<sub>4</sub>) as a reference. For this reason, acetonitrile was used as the solvent in all solution measurements.

Next, UV/vis absorption and fluorescence spectra were used to detect the reactions of 2g with phosgene, TCF, or BTC. Similar absorption and fluorescence spectra were observed from the reaction mixtures of 2g with phosgene or BTC in the absence or presence of TEA (Figure S2). The absorption spectra of the mixtures display a shorter absorption maximum (345 nm) than that of 2g. The fluorescence spectra of 2g with phosgene are similar to those with TCF or BTC, i.e., the fluorescence maximum is at 367 nm. As a comparison, Figure 1



Figure 1. Fluorescence spectra of 20  $\mu$ M 2g, 20  $\mu$ M 3g, and the reaction mixture of 20  $\mu$ M 2g solution with phosgene gas, TCF (20  $\mu$ M) or BTC (20  $\mu$ M) as well as BTC (20  $\mu$ M) in the presence of TEA (5 equiv) in CH<sub>3</sub>CN, excitation at 325 nm.

shows their fluorescence spectra of **2g** and **3g** as well as the reaction mixture of **2g** with phosgene, TCF, BTC, or BTC/ TEA in acetonitrile. Their fluorescence spectra of the reaction mixtures of **2g** with phosgene, TCF, or BTC are similar ( $\lambda_{max}$ , 367 nm) in the absence of TEA, and the fluorescence spectra of all three systems in the presence of TEA are similar to that of **3g** ( $\lambda_{max}$ , 397 nm). This indicates that the reactions of **2g** with phosgene and its substitutes in the presence of TEA generate the same end-product **3g** via similar intermediates (in the absence of TEA).

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To further observe the reaction processes, tracking experiments were performed by UV/vis absorption and fluorescence spectroscopies. In the absence of TEA, upon the addition of different amounts of BTC or TCF into 2g solution, their UV/vis absorption and fluorescence spectra display similar spectral changes, a shorter absorption band with a peak at 345 nm than that of 2g (Figure S3a), and a turn-on fluorescence centered at 367 nm with a specific structure (Figure S3b), which reveals a linear relationship with BTC or TCF in a low concentration range (Figures 2c and S3).

Upon subsequent addition of TEA (1-2 equiv), the fluorescence continuously enhances. Beginning from 3 equiv of TEA, a new fluorescence peak at 397 nm appears and enhances and reaches a maximum value at 5 equiv of TEA, and it should be assigned to 3g (Figures 2b and S2b,d).

Furthermore, the time profiles of the reactions were recorded by recording the fluorescence intensity of **2g** solution after the addition of BTC or TCF at different times. As shown in Figure S4, slow and small fluorescence response for **2g** toward BTC or TCF was observed at 367 nm (inset of Figure S4a) and 397 nm (Figure S4b), and the intensity continued to increase and reach a maximum at about 20 min. However, upon the addition of TEA, the spectral response of **2g** toward BTC is very fast, reaching a fluorescence maximum within 10 s (Figure S4b).

On the basis of the chemistry of pyridine *N*-oxides,<sup>9</sup> intermediates **A**, including **A1** (Y = CCl<sub>3</sub>O for TCF or BTC) and **A2** (Y = Cl for phosgene), were suggested and shown in Scheme 2. The nucleophilic oxygen of **2g** attacks the carbonyl of (tri/di)phosgenes, and chlorine for (di)phosgene and trichloromethoxyl for BTC are removed as a leaving group to form the intermediate **A**, chlorine ion (Cl<sup>-</sup>), or/and phosgene (COCl<sub>2</sub>). At a low TEA concentration (1–2 equiv), the increase of the fluorescence may be ascribed to the formation of phosgene, which causes **2g** to be converted to intermediate **A2**.

After the addition of TEA at high concentrations (3-10 equiv), the intermediate A2 would deprotonate to another intermediate B (Scheme 2), and subsequently convert into an ester C via a [3,3]-sigmatropic rearrangement. The ester decomposes into the final product 3g and releases CO<sub>2</sub> under the catalysis of TEA. No difference in the fluorescence spectra between C and 3g was observed (see below). This reaction was displayed to be highly efficient, and the major formation of the product 3g was observed in the reaction mixture of 2g with BTC/TEA, by HPLC analysis (Figure S5).

High-resolution mass spectra (HRMS) provide evidence for intermediates **A**, shown in Figure S6. The peaks of 349.9756 and 349.9755 were found in the reaction systems of **2g** with BTC and TCF, respectively, and were consistent with the theoretical value (349.9748,  $Y = CCl_3O$ ) of intermediate **A1**. The peak of 252.0447 was found in the mixture of **2g** with phosgene gas, which matches with the theoretical value



Figure 2. (a) UV/vis absorption and (b) fluorescence spectra of 20  $\mu$ M 2g in CH<sub>3</sub>CN upon addition of BTC (0–1 equiv), or further addition of TEA (1–10 equiv), and (c) the plot of intensity vs [BTC] of the above solutions without TEA, excitation at 325 nm.





**Figure 3.** Time-dependent fluorescence spectra of 20  $\mu$ M **2g** with 30  $\mu$ M TEA upon the addition 10  $\mu$ M BTC for 10 min, further addition of 70  $\mu$ M (a), or alternative addition of 10  $\mu$ M TEA and 10  $\mu$ M BF<sub>3</sub> solutions (b),  $\lambda_{ex}$  = 325 nm. (c) The ratio of intensity at 397 to 367 nm from (b).

(252.0422, Y = Cl) of intermediate A2. In addition, the formation of the sensing product 3g was confirmed by HRMS, a dominant m/z peak at 208.0521 was captured in the test solution, which was corresponding to  $[3g + H]^+$  (calcd 208.0524) (Figure S7).

The Boekelheide reaction is a well-established procedure.<sup>12</sup> For the classical Boekelheide reaction, the 2-picoline *N*-oxide heated with a large excess of (trifluoro)acetic anhydride is converted to the ester via a hetero-Claisen rearrangement, and after the hydrolysis of the ester, the corresponding alcohol is obtained. If 2-chloromethylpyridine is the target product, an additional step is required to chlorinate the alcohol with POCl<sub>3</sub>. The rearrangement has been explained as a radical-pair<sup>13</sup> or an ion-pair mechanism.<sup>14</sup> More current reports suggest a hetero-Claisen rearrangement or a [3,3]-sigmatropic rearrangement.<sup>15</sup>

In our system, there is no correlation between the yield of 2f and solvent polarity (Table S1). This result does not support a radical-pair or an ion-pair mechanism. In addition, an interesting reversible process provides strong evidence for the [3,3]-sigmatropic rearrangement as a pericyclic reaction. Figure 3a shows time-dependent fluorescence spectra of 2g



Figure 4. (a) UV/vis absorption and (b) fluorescence spectra of 20  $\mu$ M 2g with TEA (5 equiv) upon addition of different amounts of BTC (0–0.5 equiv), and (c) the plot of fluorescence increments at 397 nm vs the concentration of BTC from (b),  $\lambda_{ex} = 325$  nm.



**Figure 5.** Fluorescence spectra of 20  $\mu$ M **2g** with 100  $\mu$ M TEA in CH<sub>3</sub>CN after the addition of 20  $\mu$ M BTC or 100  $\mu$ M various analytes: DCP, DCNP, (COCl)<sub>2</sub>, SOCl<sub>2</sub>, SO<sub>2</sub>Cl<sub>2</sub>, POCl<sub>3</sub>, TsCl, and CH<sub>3</sub>COCl, for 2 min (a) and 15 min (b). (c) Fluorescence enhancements at 397 nm from (a) and (b), excitation at 325 nm, and a photograph of solutions in (b).

with 30  $\mu$ M TEA solution upon the addition of 10  $\mu$ M BTC. Owing to the addition of BTC for 1–2 min, a turn-on fluorescence appears at 397 nm for C and gradually shifts to 367 nm for B. Since the interaction between BTC and TEA leads to the consumption of TEA, the pericyclic reaction proceeds in the opposite direction from C to B. From 3 to 10 min, no change in the fluorescence intensity at 367 nm was observed until further addition of 70  $\mu$ M TEA, and the fluorescence peak comes back to 397 nm (Figure 3a). This reaction may proceed in different directions under different conditions: from B (or A2) to C in alkaline solutions or from C to B (or A2) in acidic solutions.

To confirm this idea, a tracking experiment was performed by the alternative addition of TEA and  $BF_3$  to the reaction mixture of **2g** with BTC. As shown in Figure 3b, after the second addition of TEA, the fluorescence peak returns to 397 nm, that is, retransformation from **B** to **C**. Upon the addition of  $BF_3$ , the fluorescence peak at 397 nm comes back to that centered at 367 nm again. This reversible process can be repeated many times when TEA and  $BF_3$  are added alternately (Figure 3c). Thus, the reaction can be "seen" as a [3,3]sigmatropic rearrangement.

As shown in Figure 3c, with the increasing number of cycles, the intensity of the peak at 397 nm (or the ratio of  $F_{397}/F_{367}$ ) enhances after the addition of TEA, and the intensity of the peak at 367 nm (or the ratio of  $F_{397}/F_{367}$ ) reduces after the addition of BF<sub>3</sub>. This implies the gradual formation of **3g** and the consumption of intermediates **A** in the cyclic processes.

**Sensing Reaction in the Detection of Phosgene.** Phosgene is a serious threat to human and public safety due to its easy availability and various ways of poisoning. Thus, it is essential to develop facile, fast, and reliable molecular probes.<sup>16</sup> In recent years, the design and synthesis of phosgene fluorescent probes have attracted extensive attention.<sup>17</sup> As described above, **2g** may be a good candidate to be used as a "turn-on" fluorescent probe for phosgene.

In the presence of 5 equiv of TEA, upon the addition of different amounts of BTC  $(0-10 \ \mu\text{M})$  into 20  $\mu\text{M}$  2g solutions, the absorption and fluorescence spectra are shown in Figure 4. A decrease in the long-wavelength band and an increase in the short-wavelength band with an isosbestic point at 350 nm (Figure 4a) show that the sensing reaction is a single and effective transformation. Meanwhile, the fluorescence spectra of 2g solutions exhibit a turn-on response with a fluorescence peak at 397 nm as shown in Figure 4b. The fluorescence intensity increases sharply with the concentration of BTC reaching an 80-fold increase after the addition of 0.5 equiv of BTC. Based on the titration experiment, the limit of detection (LOD) was found to be as low as 3.4 nM obtained from the calculation in terms of 3N/S (Figure 4c).

The response time of 2g toward phosgene and its substitutes was estimated by determining time-dependent fluorescence intensities at 397 nm of 2g with TCF, BTC, and TEA/BTC. As shown in Figure S4, the fluorescence intensity increases rapidly and reaches a plateau within 10 s for the solution of 2gwith TEA after the addition of 0.5 equiv of BTC. However, slow and small fluorescence responses at 397 nm for the

solutions of 2g without TEA upon the addition of BTC or TCF were observed at 397 nm (Figure S4b) or 367 nm (inset of Figure S4a), and the intensity continued to increase and reach a maximum at about 20 min. Therefore, specific fluorescence responses can be observed for 2g toward phosgene or its substitutes, as a slow process with a peak at 367 nm for the solution without TEA, or a rapid process with a peak at 397 nm for the solution with TEA.

To evaluate the selectivity of 2g with TEA for phosgene, fluorescence intensities at 397 nm were recorded before and after the addition of various analytes. Various relevant analytes were used to measure their fluorescence response, including nerve agent mimics (diethylchlorophosphate (DCP), diethylcyanophosphonate (DCNP)) and various acyl chlorides and analogues, oxalyl chloride ((COCl)<sub>2</sub>), thionyl chloride (SOCl<sub>2</sub>), sulfuryl chloride (SO<sub>2</sub>Cl<sub>2</sub>), phosphorus oxychloride (POCl<sub>3</sub>), tosyl chloride (TsCl), and acetyl chloride (CH<sub>3</sub>COCl). The fluorescence spectra were recorded twice: after the addition of an analyte for 2 and 15 min. Only BTC induces two different fluorescence spectra, centered at 397 nm at 2 min (Figure 5a) and 367 nm at 15 min, respectively (Figure 5b). The largest fluorescence increase of 2g solution only toward BTC, a small increase for CH<sub>3</sub>COCl, (COCl)<sub>2</sub>, and POCl<sub>3</sub>, and no significant change for other analytes were observed (Figure 5c). The fluorescence profiles show excellent selectivity for (tri)phosgene over other analytes. The sensing behavior can be easily observed by naked eyes (inset in Figure 5c). Hence, 2g displays high selectivity for phosgene over other relevant analytes.

To develop a facile, fast, and reliable detection method for phosgene gas, the test strip with 2g with trioctylamine (a tertiary amine with a higher boiling point over TEA) was prepared using polyethylene oxide, immobilizing 2g on a filter paper. A weighing bottle was used as the detection device (Figure S8). A trace phosgene solution was placed at the bottom of the bottle and the test paper was hanged in the bottle. Upon exposure to various amounts of phosgene (0–40 ppm), the test papers emit blue fluorescence under a portable UV lamp, and the fluorescence intensity increases with increasing phosgene (Figure 6). Upon exposure to 20 ppm



Figure 6. Photographs taken from 2g test strips upon exposure to various amounts of phosgene (0-40 ppm) under room light (up) or 365 nm light (down).

of phosgene gas, the test strip can produce a notable fluorescence response. According to Matheson gas data book,<sup>18</sup> the test strip with 2g can detect lower the concentration level leading to a health risk.

The selectivity of the test strip with 2g for phosgene over related analytes was also investigated. After exposure to phosgene gas or vapors of related analytes for 5 min, the test strip exposed only to phosgene emits the blue fluorescence and no observable changes can be observed for vapors of other analytes (Figure 7). These observations are completely in agreement with the results from measurements in solutions. Thus, the test strip exhibits good selectivity for phosgene over other analytes.



**Figure 7.** Photographs taken from **2g** test strips upon exposure to 40 ppm phosgene and 80 ppm of various other analytes, except for NO (1000 ppm), under room light (up) or 365 nm light (down). 0, blank; 1, phosgene (BTC/TEA); 2, DCP; 3, DCNP; 4, (COCl)<sub>2</sub>; 5, SOCl<sub>2</sub>; 6, SO<sub>2</sub>Cl<sub>2</sub>; 7, CH<sub>3</sub>COCl; 8, POCl<sub>3</sub>; 9, TsCl, in 10  $\mu$ L of chloroform solutions; and 10, NO.

#### CONCLUSIONS

In summary, we have developed a highly effective 2-methyl chlorination method of N-oxides of 2-methylpyridines, including four sets of compounds (18 substrates) with BTC in the presence of TEA at room temperature. The reactions are rapid and only HCl and CO<sub>2</sub> are generated as byproducts, and their yields are in the range of 52-95%. The reaction via a [3,3]-sigmatropic rearrangement has been demonstrated by monitoring the intermediates. The rearrangement as a reversible process, forward under alkaline conditions, and backward under acidic conditions have been observed in the reaction of 2g with BTC. Furthermore, 2g has been used as a fluorescent probe for phosgene and its substitutes with high selectivity. The sensing reaction of 2g toward phosgene, TCF, or BTC is very fast (10 s) and sensitive (3.4 nM for BTC) in the presence of TEA, and the test strip with 2g was fabricated for the rapid and selective detection of phosgene below the level leading to health risk. Therefore, the reaction of  $\alpha$ picoline-N-oxides will be effectively used in the synthesis of 2chloromethylpyridine derivatives and the design of new fluorescent probes for phosgene.

#### EXPERIMENTAL SECTION

**Materials and Instruments.** All chemicals for synthesis were purchased from commercial suppliers and used as received without further purification. <sup>1</sup>H, <sup>13</sup>C{<sup>1</sup>H}, and <sup>19</sup>F NMR spectra were measured in CDCl<sub>3</sub> or dimethyl sulfoxide (DMSO)- $d_6$  with a Bruker AV spectrometer operating at 400 or 500 MHz, 100 or 125 MHz, and 376 MHz, respectively. Chemical shifts were reported in ppm using tetramethylsilane (TMS) as the internal standard. Mass spectra were obtained with a Thermo LTQ Orbitrap mass spectrometer. UV–vis absorption and fluorescence emission spectra were recorded with a Shimadzu UV-2450 UV/vis spectrometer and a Shimadzu RF-5301pc luminescence spectrometer, respectively. The reaction mixtures of the 2-methylpyridine *N*-oxide with triphosgene were analyzed by an Agilent 1200 HPLC with a C-18 reversed-phase column.

Synthesis and Characterization of Related Compounds. Compounds 1m,<sup>19a</sup> 4,<sup>19a</sup> 2a,<sup>19b</sup> 2b,<sup>19c</sup> 2c,<sup>19d</sup> 2d,<sup>19c</sup> 2e,<sup>19e</sup> 2f,<sup>19f</sup> and  $2r^{19g}$  were obtained according to the methods in the literature. Compounds 3a,<sup>7</sup> 3b,<sup>20a</sup> 3c,<sup>20b</sup> 3d,<sup>20b</sup> 3e,<sup>20c</sup> 3f,<sup>6b</sup> and  $3r^{10}$  are the known compounds, which were obtained by the method in this work. Synthesis of tert-Butyl Ethyl(2-methylguinolin-6-yl)carbamate

Synthesis of tert-Butyl Ethyl(2-methylquinolin-o-yl)carbamate (1n). A mixture of N-ethyl-2-methylquinolin-6-amine (440 mg, 2.36 mmol), tert-butyl dicarbonate (619 mg, 2.83 mmol), and dioxane (30 mL) was stirred at 80 °C under a  $N_2$  atmosphere for 12 h. After cooling to room temperature, the solvent was evaporated to generate a crude residue, the crude product was purified by silica gel

chromatography using petroleum/acetic ether (15:1) as an eluent to isolate pure compound **1n** as a white solid (460 mg, 75%):  $R_f = 0.50$  (petroleum ether (PE)/ethyl acetate (EA) 3:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.01$  (dd, J = 8.5, 5.1 Hz, 2H, Ar–H), 7.59–7.53 (m, 2H, Ar–H), 7.29 (d, J = 8.5 Hz, 1H, Ar–H), 3.78 (q, J = 7.1 Hz, 2H, CH<sub>2</sub>), 2.76 (s, 3H, CH<sub>3</sub>), 1.45 (s, 9H, CH<sub>3</sub>), 1.20 (t, J = 7.1 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 158.8$ , 154.5, 146.0, 139.9, 136.0, 129.8, 128.9, 126.5, 123.8, 122.2, 80.4, 45.1, 28.4, 25.3; HRMS (electrospray ionization (ESI)) m/z: [M + H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> 287.1754; found 287.1752.

Synthesis of N-Ethyl-N-(2-methylquinolin-6-yl)acetamide (**10**). A mixture of N-ethyl-2-methylquinolin-6-amine (250 mg, 1.34 mmol) and Ac<sub>2</sub>O (164 mg, 1.61 mmol) in pyridine (10 mL) was stirred at 25 °C for 1 hour. After completion of the reaction time, pyridine was evaporated to generate a crude residue, which was purified by silica gel chromatography to give compound **10** as a pale yellow oil (276 mg, 90%):  $R_f = 0.43$  (PE/EA 1:3); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.09$  (t, J = 8.3 Hz, 2H, Ar–H), 7.60 (s, 1H, Ar–H), 7.49 (d, J = 8.5 Hz, 1H, Ar–H), 7.37 (d, J = 8.3 Hz, 1H, Ar–H), 3.85 (q, J = 7.0 Hz, 2H, CH<sub>2</sub>), 2.79 (s, 3H, CH<sub>3</sub>), 1.88 (s, 3H, CH<sub>3</sub>), 1.16 (t, J = 6.9 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 170.0$ , 160.0, 146.7, 140.0, 136.1, 130.4, 129.8, 126.7, 126.3, 122.9, 44.0, 25.3, 23.0, 13.1; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>N<sub>2</sub>O 229.1335; found 229.1332.

Synthesis of N-Ethyl-2,2,2-trifluoro-N-(2-methylquinolin-6-yl)acetamide (1p). A mixture of N-ethyl-2-methylquinolin-6-amine (330 mg, 1.77 mmol), triethylamine (233 mg, 2.30 mmol), and DCM (15 mL) was stirred at 0 °C for 10 min, and then trifluoroacetic anhydride (TFAA) (485 mg, 2.30 mmol) was added dropwise to the mixture over 30 min. The solution was stirred at room temperature until the thin-layer chromatography (TLC) showed no raw material. After completion of the reaction time, the solution was washed with saturated aqueous NaHCO<sub>3</sub> solution  $(1 \times 5 \text{ mL})$ , the organic phase was then dried over anhydrous Na2SO4. The filtrate was evaporated to afford a crude product, which was purified by silica gel chromatography to give compound 1p as a yellow liquid (400 mg, 80%):  $R_f = 0.46$  (PE/EA 2:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.09$  (t, J = 7.7 Hz, 2H, Ar–H), 7.64 (d, J = 1.5 Hz, 1H, Ar-H), 7.51 (dd, J = 8.9, 2.3 Hz, 1H, Ar-H), 7.38 (d, J = 8.5 Hz, 1H, Ar-H), 3.88 (s, 2H, CH<sub>2</sub>), 2.79 (s, 3H, CH<sub>3</sub>), 1.24 (t, J = 7.2 Hz, 3H, CH<sub>3</sub>);  ${}^{13}C{}^{1}H$  NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  = 160.7, 156.5 (q,  ${}^{2}J_{C-F}$  = 35.7 Hz), 147.2, 136.3, 135.9, 130.4, 129.3, 127.1, 126.2, 123.1, 116.3 (q,  ${}^{1}J_{C-F}$  = 288.5 Hz), 46.9, 25.4, 12.2;  ${}^{19}F$  NMR (376 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  = -67.2; HRMS (ESI) *m/z*: [M + H]<sup>+</sup> calcd for  $C_{14}H_{14}F_3N_2O$  283.1053; found 283.1054.

Synthesis of 2,2,2-Trifluoro-N-(2-methylquinolin-6-yl)acetamide (1q). Following the same procedure as for the synthesis of 1p, using 2-methylquinolin-6-amine (500 mg, 3.18 mmol), triethylamine (420 mg, 4.13 mmol), and TFAA (870 mg, 4.13 mmol) as materials in 20 mL DCM, 1q was obtained as a white solid (570 mg, 70%):  $R_f = 0.46$  (PE/EA 2:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.90$  (s, 1H, Ar–H), 8.33 (d, J = 2.4 Hz, 1H, Ar–H), 8.03 (d, J = 8.5 Hz, 1H, Ar–H), 7.98 (d, J = 9.0 Hz, 1H, Ar–H), 7.64 (dd, J = 9.0, 2.5 Hz, 1H, Ar–H), 7.32 (d, J = 8.5 Hz, 1H, Ar–H), 2.74 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 159.3$ , 155.2 (q,  ${}^2J_{C-F} = 37.6$  Hz), 145.7, 136.3, 132.5, 129.7, 126.7, 123.1, 122.9, 117.9, 115.7 (q,  $J_{C-F} = 289.78$  Hz), 25.1; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = -75.5$ ; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>10</sub>F<sub>3</sub>N<sub>2</sub>O 255.0740; found 255.0743.

General Method for the Synthesis of 2-Methylpyridine N-Oxide Derivatives (2). 2-Methylpyridine (2.66 mmol, 1.0 equiv) was dissolved in DCM (20 mL) and cooled to 0 °C. Next, 85% 3chloroperbenzoic acid (*m*-CPBA) (2.66 mmol, 1.0 equiv) was added to the solution in portions over 30 min and then stirred for 12 h at room temperature. Finally, solid  $K_2CO_3$  (3.99 mmol, 1.5 equiv) was added, and the resulting mixture was stirred for an additional 30 min. The solid was separated by filtration, and the filtrate was evaporated to afford a crude product, which was purified by silica gel chromatography to give 2-methylpyridine N-oxide. Synthesis of 7-Methoxy-2-methylquinoline 1-Oxide (**2g**). Following the same general procedure as for the synthesis of **2**, compound **2g** was obtained as a pale yellow solid (447 mg, 89%):  $R_f = 0.40$  (MeOH/DCM 1:20); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.14$  (d, J = 2.4 Hz, 1H, Ar–H), 7.72 (d, J = 8.9 Hz, 1H, Ar–H), 7.61 (d, J = 8.4 Hz, 1H, Ar–H), 7.24–7.19 (m, 2H, Ar–H), 4.01 (s, 3H, CH<sub>3</sub>), 2.74 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 162.0$ , 146.5, 142.8, 129.3, 125.5, 124.2, 120.7, 120.4, 98.2, 55.9, 18.9; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>12</sub>NO<sub>2</sub> 190.0863; found 190.0863.

Synthesis of 2-Methyl-7-(trifluoromethyl)quinoline 1-Oxide (2h). Following the same general procedure as for the synthesis of 2, compound 2h was obtained as a white solid (534 mg, 88%):  $R_f = 0.43$  (MeOH/DCM 1:20); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  = 9.11 (s, 1H, Ar–H), 7.98 (d, J = 8.5 Hz, 1H, Ar–H), 7.79 (dd, J = 8.5, 1.6 Hz, 1H, Ar–H), 7.72 (d, J = 8.6 Hz, 1H, Ar–H), 7.79 (dd, J = 8.6 Hz, 1H, Ar–H), 7.47 (d, J = 8.6 Hz, 1H, Ar–H), 2.76 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  = 147.1, 141.0, 132.0 (q,  $J_{C-F} = 33.3$  Hz), 130.8, 129.4, 125.2, 124.4, 123.7 (q,  $J_{C-F} = 3.2$  Hz), 124.6 (q,  $J_{C-F} = 273.9$  Hz), 118.0 (q,  $J_{C-F} = 4.6$  Hz), 18.8; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  = -62.6; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>9</sub>F<sub>3</sub>NO 228.0631; found 228.0630.

Synthesis of 6-(Diethylamino)-2-methylquinoline 1-Oxide (2i). A mixture of acetaldehyde (150 mg, 3.40 mmol) and 3 M  $\rm H_2SO_4$  (0.2 mL) was stirred in tetrahydrofuran (THF) at 0 °C for 10 min and then added to the solution of 2k (100 mg, 0.49 mmol) in THF (5 mL) and NaBH<sub>4</sub> (40 mg, 1.06 mmol). The mixture was stirred at room temperature for 5 h. The residue was neutralized with ammonia, and the organic phase was dried with MgSO4, and the filtrate was evaporated to afford a crude product. The crude product was purified by column chromatography to afford compound 2i as a brown oil (64 mg, 56%):  $R_f = 0.54$  (MeOH/DCM 1:20); <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ , 25 °C, TMS):  $\delta$  = 8.57 (d, J = 9.7 Hz, 1H, Ar–H), 7.44 (d, J = 8.6 Hz, 1H, Ar-H), 7.25 (d, J = 2.7 Hz, 1H, Ar-H), 7.14 (d, J = 8.6 Hz, 1H, Ar–H), 6.74 (d, J = 2.3 Hz, 1H, Ar–H), 3.46 (q, J = 7.1 Hz, 4H, CH<sub>2</sub>), 2.65 (s, 3H, CH<sub>3</sub>), 1.23 (t, J = 7.1 Hz, 6H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  = 146.6, 141.5, 134.5, 131.2, 124.3, 123.0, 120.5, 118.8, 104.1, 44.7, 18.3, 12.5; HRMS (ESI) m/z:  $[M + H]^+$  calcd for C<sub>14</sub>H<sub>19</sub>N<sub>2</sub>O 231.1492; found 231.1492

Synthesis of 6-(Ethyl(methyl)amino)-2-methylquinoline 1-Oxide (2j). A mixture of 37% formaldehyde solution (60 mg, 3.40 mmol) and 3 M  $H_2SO_4~(0.2~mL)$  was stirred in THF at 0  $^\circ C$  for 10 min and then added to the solution of 2k (100 mg, 0.49 mmol) in THF (5 mL) and NaBH<sub>4</sub> (40 mg, 1.06 mmol). The mixture was stirred at room temperature for 5 h. The residue was neutralized with ammonia, and the organic phase was dried with MgSO4, and the filtrate was evaporated to afford a crude product. The crude product was purified by column chromatography to afford compound 2j as a yellow oil (60 mg, 56%):  $R_f = 0.49$  (MeOH/DCM 1:20); <sup>1</sup>H NMR (400 MHz,  $\dot{\text{CDCl}}_3$ , 25 °C, TMS):  $\delta$  = 8.59 (d, J = 9.6 Hz, 1H, Ar–H), 7.43 (d, J = 8.6 Hz, 1H, Ar-H), 7.29 (dd, J = 9.6, 2.6 Hz, 1H, Ar-H), 7.14 (d, J = 8.6 Hz, 1H, Ar-H), 6.73 (d, J = 2.6 Hz, 1H, Ar-H), 3.51 (q, J = 7.1 Hz, 2H, CH<sub>2</sub>), 3.02 (s, 3H, CH<sub>3</sub>), 2.65 (s, 3H, CH<sub>3</sub>), 1.18 (t, J = 7.1Hz, 3H, CH<sub>3</sub>);  ${}^{13}C{}^{1}H$  NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta =$ 154.3, 146.7, 141.7, 134.3, 129.2, 128.0, 122.1, 119.2, 105.2, 47.1, 37.7, 24.9, 11.4; HRMS (ESI) m/z:  $[M + H]^+$  calcd for  $C_{13}H_{17}N_2O$ 217.1335; found 217.1332.

Synthesis of 6-(Ethylamino)-2-methylquinoline 1-Oxide (**2k**). Compound **2p** (300 mg, 1.00 mmol) and NaOEt (680 mg, 10.00 mmol) were dissolved in EtOH (10 mL). The mixture was stirred at 54 °C. After 20 h, the reaction mixture was allowed to cool to room temperature, CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and saturated ammonium chloride solution (5 mL) were added and the phases were separated. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated, which was purified by silica gel chromatography to give compound **2k** as a yellow solid (150 mg, 75%):  $R_f = 0.24$  (MeOH/DCM 1:20); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.53$  (d, J = 9.4 Hz, 1H, Ar–H), 7.42 (d, J = 8.6 Hz, 1H, Ar–H), 7.15 (d, J = 8.6 Hz, 1H, Ar–H), 7.06 (dd, J = 9.4, 2.5 Hz, 1H, Ar–H), 6.66 (d, J = 2.5 Hz, 1H, Ar–H), 3.23 (q, J = 7.2 Hz, 2H, CH<sub>2</sub>), 2.64 (s, 3H, CH<sub>3</sub>), 1.32 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  = 147.2, 141.8, 135.7, 131.2, 124.0, 123.1, 121.4, 120.4, 103.0, 38.3, 18.3, 14.5; HRMS (ESI) *m*/*z*: [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>O 203.1179; found 203.1180.

Synthesis of 6-Amino-2-methylquinoline 1-Oxide (21). Using compound 2q (270 mg, 1.00 mmol), NaOEt (680 mg, 10.00 mmol), and EtOH (10 mL) as materials to follow the same procedure as for the synthesis of 2k, compound 2l was obtained as a yellow solid (155 mg, 89%):  $R_f = 0.46$  (MeOH/DCM 1:30); <sup>1</sup>H NMR (400 MHz, DMSO, 25 °C, TMS):  $\delta = 8.26$  (d, J = 9.2 Hz, 1H, Ar–H), 7.46 (d, J = 8.6 Hz, 1H, Ar–H), 7.31 (d, J = 8.6 Hz, 1H, Ar–H), 7.13 (d, J = 9.3 Hz, 1H, Ar–H), 6.83 (d, J = 2.2 Hz, 1H, Ar–H), 5.77 (s, 2H, NH<sub>2</sub>), 2.46 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSO, 25 °C, TMS):  $\delta = 148.5$ , 140.4, 134.7, 131.4, 123.7, 122.6, 121.6, 120.1, 105.9, 18.2; HRMS (ESI) m/z:  $[M + H]^+$  calcd for C<sub>10</sub>H<sub>11</sub>N<sub>2</sub>O 175.0866; found 175.0869.

Synthesis of 6-(tert-Butoxycarbonyl(butyl)amino)-2-methylquinoline 1-Oxide (**2m**). Following the same general procedure as for the synthesis of **2**, **2m** was obtained as a pale yellow solid (819 mg, 93%):  $R_f = 0.53$  (MeOH/DCM 1:20); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.72$  (d, J = 9.2 Hz, 1H, Ar–H), 7.64 (t, J = 8.9 Hz, 3H, Ar–H), 7.33 (d, J = 8.5 Hz, 1H, Ar–H), 3.74 (t, J = 3.7 Hz, 2H, CH<sub>2</sub>), 2.73 (s, 3H, CH<sub>3</sub>), 1.59–1.52 (m, 2H, CH<sub>2</sub>), 1.45 (s, 9H, CH<sub>3</sub>), 1.35–1.30 (m, 2H, CH<sub>2</sub>), 0.90 (t, J = 7.4 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 154.3$ , 145.9, 142.2, 139.4, 130.5, 129.5, 125.4, 123.9, 123.4, 120.1, 80.8, 49.8, 30.7, 28.3, 19.9, 18.8, 13.8; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub> 331.2016; found 331.2012.

Synthesis of 6-(tert-Butoxycarbonyl(ethyl)amino)-2-methylquinoline 1-Oxide (**2n**). Following the same general procedure as for the synthesis of **2**, **2n** was obtained as a pale yellow solid (645 mg, 80%):  $R_f = 0.52$  (MeOH/DCM 1:20); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.72$  (d, J = 9.2 Hz, 1H, Ar–H), 7.66–7.62 (m, 3H, Ar– H), 7.32 (t, J = 7.1 Hz, 1H, Ar–H), 3.80 (q, J = 7.1 Hz, 2H, CH<sub>2</sub>), 2.74 (s, 3H, CH<sub>3</sub>), 1.45 (s, 9H, CH<sub>3</sub>), 1.21 (t, J = 7.1 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 154.1$ , 145.9, 142.1, 139.4, 130.4, 129.5, 125.4, 123.8, 123.4, 120.2, 80.9, 45.0, 28.3, 18.8, 14.0; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub> 303.1703; found 303.1703.

Synthesis of 6-(*N*-Ethylacetamido)-2-methylquinoline 1-Oxide (**20**). Following the same general procedure as for the synthesis of **2**, **20** was obtained as a pale yellow solid (600 mg, 92%):  $R_f = 0.35$  (MeOH/DCM 1:20); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.85$  (d, J = 9.1 Hz, 1H, Ar–H), 7.66 (dd, J = 5.0, 3.3 Hz, 2H, Ar–H), 7.55 (d, J = 9.2 Hz, 1H, Ar–H), 7.41 (d, J = 8.6 Hz, 1H, Ar–H), 3.85 (q, J = 7.1 Hz, 2H, CH<sub>2</sub>), 2.73 (d, J = 16.0 Hz, 3H, CH<sub>3</sub>), 1.87 (s, 3H, CH<sub>3</sub>), 1.16 (t, J = 7.0 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 169.6$ , 146.5, 142.2, 140.6, 130.5, 129.8, 126.7, 124.6, 124.2, 121.8, 44.0, 23.0, 18.8, 13.2; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub> 245.1285; found 245.1281.

Synthesis of 6-(*N*-Ethyl-2,2,2-trifluoroacetamido)-2-methylquinoline 1-Oxide (**2p**). Following the same general procedure as for the synthesis of **2**, compound **2p** was obtained as a white solid (692 mg, 87%):  $R_f = 0.60$  (MeOH/DCM 1:20); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.87$  (d, J = 9.2 Hz, 1H, Ar–H), 7.71 (s, 1H, Ar– H), 7.67 (d, J = 8.6 Hz, 1H, Ar–H), 7.58 (dd, J = 9.2, 2.0 Hz, 1H, Ar–H), 7.43 (d, J = 8.6 Hz, 1H, Ar–H), 3.89 (d, J = 5.8 Hz, 2H, CH<sub>2</sub>), 2.75 (s, 3H, CH<sub>3</sub>), 1.24 (t, J = 7.1 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 156.3$  (q,  $J_{C-F} = 36.0$ Hz), 147.2, 141.1, 138.1, 130.1, 129.3, 127.6, 124.8, 124.5, 121.8, 116.2 (q,  $J_{C-F} = 298.2$  Hz), 46.9, 18.9, 12.3; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = -67.1$ ; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> 299.1002; found 299.1004.

Synthesis of 2-Methyl-6-(2,2,2-trifluoroacetamido)quinoline 1-Oxide (**2q**). Following the same general procedure as for the synthesis of **2**, compound **2q** was obtained as a white solid (534 mg, 74%):  $R_f$  = 0.26 (MeOH/DCM 1:20); <sup>1</sup>H NMR (400 MHz, DMSO, 25 °C, TMS):  $\delta$  = 11.67 (s, 1H, NH), 8.57 (d, *J* = 9.4 Hz, 1H, Ar–H), 8.44 (d, *J* = 2.2 Hz, 1H, Ar–H), 7.97 (dd, *J* = 9.4, 2.3 Hz, 1H, Ar–H), 7.86 (d, *J* = 8.6 Hz, 1H, Ar–H), 7.59 (d, *J* = 8.6 Hz, 1H, Ar–H), 2.56 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSO, 25 °C, TMS):  $\delta$  = 155.4 (q, *J*<sub>C–F</sub> = 37.4 Hz), 145.1, 138.8, 136.0, 129.7, 124.8, 124.6, 124.4, 120.4, 118.9, 116.1 (q, *J*<sub>C–F</sub> = 289.6 Hz), 18.5; <sup>19</sup>F NMR (376 MHz, DMSO, 25 °C, TMS):  $\delta$  = -73.9; HRMS (ESI) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>10</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> 271.0689; found 271.0691.

General Method for the Synthesis of 2-Chloromethylpyridine Derivatives (3). Compound 2 (2.11 mmol, 1.0 equiv) and TEA (10.55 mmol, 5.0 equiv) were dissolved in DCM (20 mL) under a  $N_2$ atmosphere and cooled to 0 °C. Next, the DCM solution (2 mL) of triphosgene (1.06 mmol, 0.5 equiv) was added to the solution in portions over 10 min. After removing the ice bath, the solution was stirred for 20 min at room temperature. The reaction mixture was adjusted to neutral with NaHCO<sub>3</sub> solution and then extracted with DCM (2 × 10 mL). The organic phase was washed with water twice, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, and filtered, and the solvent was removed in vacuo. The residue was chromatographed on silica gel to get the corresponding 2-chloromethylpyridine derivatives 3.

Compounds 3a-f and 3r were prepared by following the same general procedure as for the synthesis of 3: 3a as a yellow oil (151 mg, 56%), 3b as a yellow oil (105 mg, 35%), 3c as a pale red oil (114 mg, 38%), 3d as a claybank oil (90 mg, 30%), 3e as a yellow oil (127 mg, 36%), 3f as a pale yellow oil (210 mg, 56%), and 3r as a white solid (189 mg, 37%).

Synthesis of 2-(Chloromethyl)-7-methoxyquinoline (**3g**). Following the same general procedure as for the synthesis of **3**, **3g** was obtained as a pale yellow solid (285 mg, 65%):  $R_f = 0.60$  (PE/EA 6:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.12$  (d, J = 8.3 Hz, 1H, Ar–H), 7.70 (d, J = 9.0 Hz, 1H, Ar–H), 7.47 (d, J = 8.3 Hz, 1H, Ar–H), 7.41 (d, J = 2.3 Hz, 1H, Ar–H), 7.22 (dd, J = 8.9, 2.5 Hz, 1H, Ar–H), 4.82 (s, 2H, CH<sub>2</sub>–Cl), 3.95 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 161.2$ , 156.8, 149.1, 137.1, 128.6, 122.7, 120.4, 118.3, 106.9, 55.6, 47.2; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>11</sub>ClNO 208.0524; found 208.0523.

Synthesis of 2-Methyl-7-(trifluoromethyl)quinoline 1-Oxide (**3h**). Following the same general procedure as for the synthesis of **3**, **3h** was obtained as a pale green solid (265 mg, 51%):  $R_f = 0.65$  (PE/EA 6:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.42$  (d, J = 0.8 Hz, 1H, Ar–H), 8.29 (d, J = 8.5 Hz, 1H, Ar–H), 7.97 (d, J = 8.5 Hz, 1H, Ar–H), 7.97 (d, J = 8.5 Hz, 1H, Ar–H), 7.97 (d, J = 8.5 Hz, 2H, Ar–H), 4.87 (s, 2H, CH<sub>2</sub>–Cl); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 158.3$ , 146.4, 137.2, 131.8 (q,  $J_{C-F} = 32.9$  Hz), 128.8, 128.8, 127.1 (q,  $J_{C-F} = 4.5$  Hz), 123.8 (q,  $J_{C-F} = 273.6$  Hz), 122.7 (q,  $J_{C-F} = 3.0$  Hz), 122.4, 46.9; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = -62.7$ ; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>8</sub>ClF<sub>3</sub>N 246.0292; found 246.0293.

Synthesis of 2-(Chloromethyl)-N,N-diethylquinolin-6-amine (**3i**). Following the same general procedure as for the synthesis of **3**, **3i** was obtained as a yellow oil (226 mg, 43%):  $R_f = 0.65$  (PE/EA 6:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 7.91$  (dd, J = 13.2, 9.0 Hz, 2H, Ar–H), 7.42 (d, J = 8.5 Hz, 1H, Ar–H), 7.30 (dd, J = 9.4, 2.8 Hz, 1H, Ar–H), 6.75 (d, J = 2.5 Hz, 1H, Ar–H), 4.79 (s, 2H, CH<sub>2</sub>–Cl), 3.47 (q, J = 7.1 Hz, 4H, CH<sub>2</sub>), 1.23 (t, J = 7.1 Hz, 6H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  151.5, 146.3, 140.8, 135.0, 129.9, 129.5, 120.8, 119.3, 103.7, 47.7, 44.7, 12.6; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>18</sub>ClN<sub>2</sub> 249.1153; found 249.1150.

Synthesis of 2-(Chloromethyl)-N-ethyl-N-methylquinolin-6amine (**3***j*). Following the same general procedure as for the synthesis of **3**, **3***j* was obtained as a yellow oil (134 mg, 27%):  $R_f = 0.54$  (PE/EA 1:3); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 7.90$  (d, J = 8.5Hz, 1H, Ar–H), 7.86 (d, J = 9.4 Hz, 1H, Ar–H), 7.38 (d, J = 8.5 Hz, 1H, Ar–H), 7.29 (dd, J = 9.4, 2.8 Hz, 1H, Ar–H), 6.70 (d, J = 2.8 Hz, 1H, Ar–H), 4.74 (s, 2H, CH<sub>2</sub>), 3.46 (q, J = 7.1 Hz, 2H, CH<sub>2</sub>), 2.97 (s, 3H, CH<sub>3</sub>), 1.12 (t, J = 7.1 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 151.8$ , 147.6, 140.9, 135.3, 129.6, 129.3, 120.9, 119.6, 104.4, 47.6, 47.0, 37.7, 11.5; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>16</sub>ClN<sub>2</sub> 235.0997; found 235.1002.

Synthesis of 2-(Chloromethyl)-N-ethylquinolin-6-amine (3k). Following the same general procedure as for the synthesis of 3, 3k was obtained as a pale yellow solid (247 mg, 53%):  $R_f = 0.55$  (PE/EA

3:1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  = 8.23 (d, *J* = 8.5 Hz, 1H, Ar–H), 8.15 (d, *J* = 8.9 Hz, 1H, Ar–H), 7.72 (s, 1H, Ar–H), 7.70 (d, *J* = 3.2 Hz, 1H, Ar–H), 7.58 (d, *J* = 8.4 Hz, 1H, Ar–H), 4.85 (s, 2H, CH<sub>2</sub>–Cl), 3.90 (s, 2H, CH<sub>2</sub>), 1.27 (t, *J* = 6.7 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS)  $\delta$  158.0, 146.6, 139.8, 137.4, 131.0, 130.3, 127.5, 126.9, 121.4, 48.3, 47.1, 13.0; HRMS (ESI) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>14</sub>ClN<sub>2</sub> 221.0840; found 221.0840.

Synthesis of 2-(Chloromethyl)quinolin-6-amine (**3**). Following the same general procedure as for the synthesis of **3**, **3**I was obtained as a yellow solid (118 mg, 29%):  $R_f = 0.5$  (PE/EA 2:1); <sup>1</sup>H NMR (400 MHz, DMSO, 25 °C, TMS):  $\delta = 8.01$  (d, J = 8.5 Hz, 1H, Ar–H), 7.72 (d, J = 9.0 Hz, 1H, Ar–H), 7.44 (t, J = 5.3 Hz, 1H, Ar–H), 7.21 (dt, J = 8.9, 4.4 Hz, 1H, Ar–H), 6.84 (d, J = 2.5 Hz, 1H, Ar–H), 4.86 (s, 2H, CH<sub>2</sub>–Cl); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSO, 25 °C, TMS):  $\delta = 151.4$ , 147.9, 141.2, 134.9, 129.7, 129.6, 122.7, 121.6, 105.3, 48.1; HRMS (ESI) m/z:  $[M + H]^+$  calcd for C<sub>10</sub>H<sub>10</sub>ClN<sub>2</sub> 193.0527; found 193.0528.

Synthesis of tert-Butyl Butyl(2-(chloromethyl)quinolin-6-yl)carbamate (**3m**). Following the same general procedure as for the synthesis of **3**, **3m** was obtained as a white solid (472 mg, 64%):  $R_f =$ 0.68 (PE/EA 3:1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta =$ 8.15 (d, *J* = 8.5 Hz, 1H, Ar–H), 8.03 (d, *J* = 8.8 Hz, 1H, Ar–H), 7.61 (dd, *J* = 13.1, 5.5 Hz, 3H, Ar–H), 4.84 (s, 2H, CH<sub>2</sub>–Cl), 3.75 (t, *J* = 7.5 Hz, 2H, CH<sub>2</sub>), 1.59–1.53 (m, 2H, CH<sub>2</sub>), 1.45 (s, 9H, CH<sub>3</sub>), 1.37–1.29 (m, 2H, CH<sub>2</sub>), 0.90 (t, *J* = 7.4 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta =$  156.5, 154.5, 145.5, 141.2, 137.1, 130.4, 129.5, 127.5, 123.6, 120.8, 80.6, 49.9, 47.3, 30.7, 28.3, 19.9, 13.8; HRMS (ESI) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>26</sub>ClN<sub>2</sub>O<sub>2</sub> 349.1677; found 349.1671.

Synthesis of tert-Butyl 2-(Chloromethyl)quinolin-6-yl(ethyl)carbamate (**3n**). Following the same general procedure as for the synthesis of **3**, **3n** was obtained as a brown solid (407 mg, 60%):  $R_f =$ 0.50 (PE/EA 6:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta =$ 8.16 (d, *J* = 8.5 Hz, 1H, Ar–H), 8.03 (d, *J* = 8.8 Hz, 1H, Ar–H), 7.63 – 7.60 (m, 3H, Ar–H), 4.84 (s, 2H, CH<sub>2</sub>–Cl), 3.80 (q, *J* = 7.1 Hz, 2H, CH<sub>2</sub>), 1.46 (s, 9H, CH<sub>3</sub>), 1.21 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta =$  156.5, 154.3, 145.4, 141.1, 137.1, 130.4, 129.5, 127.6, 123.5, 120.8, 80.6, 47.2, 45.1, 28.4, 14.0; HRMS (ESI) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>22</sub>ClN<sub>2</sub>O<sub>2</sub> 321.1364; found 321.1366.

Synthesis of N-(2-(Chloromethyl)quinolin-6-yl)-N-ethylacetamide (**30**). Following the same general procedure as for the synthesis of **3**, **30** was obtained as a pale yellow oil (489 mg, 88%):  $R_f = 0.5$ (PE/EA 1:2); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.23$ (d, J = 8.5 Hz, 1H, Ar–H), 8.15 (d, J = 8.9 Hz, 1H, Ar–H), 7.69 (d, J = 8.5 Hz, 1H, Ar–H), 7.65 (d, J = 2.1 Hz, 1H, Ar–H), 7.55 (dd, J = 8.9, 2.2 Hz, 1H, Ar–H), 4.86 (s, 2H, CH<sub>2</sub>–Cl), 3.86 (q, J = 7.1 Hz, 2H, CH<sub>2</sub>), 1.88 (s, 3H, CH<sub>3</sub>), 1.17 (t, J = 7.1 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 169.8$ , 157.7, 146.3, 141.2, 137.3, 131.1, 130.4, 127.7, 126.3, 121.4, 47.1, 44.0, 23.0, 13.2; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>16</sub>ClN<sub>2</sub>O 263.0946; found 263.0942.

Synthesis of N-(2-(Chloromethyl)quinolin-6-yl)-N-ethyl-2,2,2-trifluoroacetamide (**3p**). Following the same general procedure as for the synthesis of **3**, **3p** was obtained as a pale yellow oil (495 mg, 74%):  $R_f = 0.48$  (PE/EA 3:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = 8.25$  (d, J = 8.5 Hz, 1H, Ar–H), 8.16 (d, J = 8.9 Hz, 1H, Ar–H), 7.71 (d, J = 8.5 Hz, 2H, Ar–H), 7.57 (dd, J = 8.9, 2.3 Hz, 1H, Ar–H), 4.86 (s, 2H, CH<sub>2</sub>–Cl), 3.90 (s, 2H, CH<sub>2</sub>), 1.24 (t, J = 7.2 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta =$ 158.3, 156.4 (q, <sup>2</sup> $J_{C-F} = 35.8$  Hz), 146.8, 137.5, 137.1, 131.1, 129.9, 127.2, 127.2, 121.6, 117.7 (q,  $J_{C-F} = 289.5$  Hz), 47.0, 46.9, 12.3; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta = -67.1$ ; HRMS (ESI) m/z: [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>13</sub>ClF<sub>3</sub>N<sub>2</sub>O 317.0663; found 317.0660.

Synthesis of N-(2-(Chloromethyl)quinolin-6-yl)-2,2,2-trifluoroacetamide (**3q**). Following the same general procedure as for the synthesis of **3**, **3q** was obtained as a pale yellow solid (305 mg, 50%):  $R_f = 0.54$  (PE/EA 5:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$ = 8.22 (d, J = 8.5 Hz, 1H, Ar–H), 8.15 (d, J = 8.9 Hz, 1H, Ar–H), 7.66 (d, *J* = 8.5 Hz, 1H, Ar–H), 7.51 (d, *J* = 2.1 Hz, 1H, Ar–H), 7.48 (dd, *J* = 8.9, 2.3 Hz, 1H, Ar–H), 4.85 (s, 2H, CH<sub>2</sub>–Cl);  $^{13}C{^{1}H}$ NMR (125 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  = 157.4, 146.1, 141.8, 137.4, 133.6 (q, *J* = 43.6 Hz), 130.7, 127.5, 123.8, 121.5, 117.8, 116.8 (q, <sup>1</sup>*J* = 278.1 Hz), 47.1;  $^{19}$ F NMR (376 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  = -71.6; HRMS (ESI) *m*/*z*: [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>9</sub>ClF<sub>3</sub>N<sub>2</sub>O 289.0350; found 289.0353.

Synthesis of N-Ethyl-2-methylquinolin-6-amine (5).<sup>21</sup> A mixture of 2-methylquinolin-6-amine (500 mg, 3.16 mmol), iodoethane (592 mg, 3.79 mmol), K<sub>2</sub>CO<sub>3</sub>(1.1 g, 7.9 mmol), and dimethylformamide (DMF) (15 mL) was stirred at 80 °C, refluxed until the TLC showed that no raw material exists. After cooling to room temperature, the mixture was extracted with dichloromethane (10 mL × 3), the organic phases were combined, then washed with water, and dried over MgSO<sub>4</sub>. The filtrate was evaporated to generate a crude residue, and the crude product was purified by silica gel chromatography using petroleum/acetic ether (5:1) as an eluent to isolate compound **5** as a yellow oil (342 mg, 58%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  = 7.81 (t, *J* = 9.4 Hz, 2H, Ar–H), 7.15 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.05 (dd, *J* = 9.0, 2.6 Hz, 1H, Ar–H), 6.68 (d, *J* = 2.6 Hz, 1H, Ar–H), 3.82 (s, 1H, NH), 3.24 (q, *J* = 7.1 Hz, 2H, CH<sub>2</sub>), 2.66 (s, 3H, CH<sub>3</sub>), 1.32 (t, 3H, *J* = 7.1 Hz, CH<sub>3</sub>).

**HPLC Analysis of the Yields of 2-Methylpyridine** *N***-Oxides with Triphosgene.** The reaction mixtures of the 2-methylpyridine *N*-oxide with triphosgene were analyzed by an Agilent 1200 HPLC with a C-18 reversed-phase column. A solution of 0.1 mM 2-methylpyridine *N*-oxide with 0.5 mM TEA was placed into a centrifuge tube, then 0.05 mM triphosgene solution was added for 10 min, and finally analyzed by HPLC. First, pure compounds 2 and 3 were analyzed, the chromatographic peaks were assigned, and the standard curve between the peak area and the concentration was obtained. Then, the reaction mixture was analyzed and the yield was obtained.

**Preparation of the 2g Test Paper. 2g** (2 mg) with trioctylamine (3.74 mg) were dissolved in 20 mL of DCM. Then, poly(ethylene oxide) (1.5 g) was added in batches. The mixture was stirred until poly(ethylene oxide) dissolved completely. The filter paper was immersed in the solution and then taken out to dry in air. Finally, the paper with **2g** was cut into strips  $(1.0 \times 2.0 \text{ cm}^2)$  as the test paper for the detection of phosgene in the gas phase.

Detection of the Gaseous Phase with the Testing Paper. Detection of Phosgene Gas in Various Concentrations. Four concentrations of triphosgene solutions, 0.97, 1.94, 2.90, and 3.87 mM, were prepared with DCM as a solvent, and 10  $\mu$ L of solutions were added to a container (65 mL) with an HPLC injection needle, followed by the addition of 10  $\mu$ L of DCM containing 0.1% TEA, respectively, and finally the container was closed. After 5 min, a photograph of the fluorescence of the test papers together with a blank was taken under 365 nm light.

Selective Detection of Phosgene Gas over Vapor of Other Analytes. DCM solutions of triphosgene (3.87 mM), NO (65  $\mu$ L), and other analytes (23.21 mM) containing DCP, DCNP, (COCl)<sub>2</sub>, SOCl<sub>2</sub>, SO<sub>2</sub>Cl<sub>2</sub>, CH<sub>3</sub>COCl, POCl<sub>3</sub>, and TsCl were prepared. Using an HPLC injection needle, 10  $\mu$ L of the above solution was placed at the bottom of a weighing bottle, respectively (see the legend in Figure S8). The concentration of analytes was calculated to be 40 ppm for phosgene, 1000 ppm for NO, and 80 ppm for others.

#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00749.

Optimization of the reaction conditions; screening of solvents in the reaction; spectral response of 2g toward phosgene and its substitutes; HPLC analysis; HRMS for the reaction mixture; detection in the gas phase; and synthesis routes of related compounds as well as their copies for NMR spectra (PDF)

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# **Author Contributions**

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#### Notes

The authors declare no competing financial interest.

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