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Heterocycle Functionalization

# Hydroxymethylation of Quinolines with $Na_2S_2O_8$ by a Radical Pathway

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**Abstract:** Quinolines and isoquinolines were treated with $Na_2S_2O_8$ in a mixture of methanol and water at 70 °C to form hydroxymethylated quinolines and isoquinolines in good to moderate yields, under transition-metal-free conditions. The formed hydroxymethyl group was smoothly converted into aldehyde, ester, amide, bromomethyl, (*N*,*N*-diethylamino)methyl, cyano, and tetrazole groups, in good yields.

## Introduction

Synthetic studies of quinolines bearing a hydroxymethyl group are very attractive and important, because most quinoline derivatives show biological activities. For example, quinoline derivative **I** shows significant cytotoxicity,[1a] and renierol **II** is a potent inhibitor of xanthine oxidase (Figure 1).[1b] Moreover, the hydroxymethyl group can be easily transformed into various different functional groups.

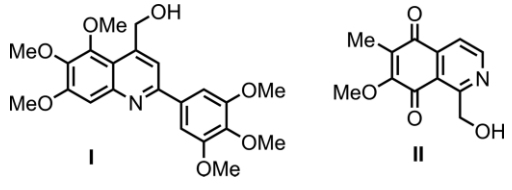


Figure 1. Quinoline derivatives containing a hydroxymethyl group.

Today, many methods are known for the introduction of alkyl groups into quinolines through radical pathways.[2] Examples of such methods include the decarboxylative alkylation of quinolines with alkanoic acids, $AgNO_3$, and $K_2S_2O_8$ under heating conditions (the Minisci reaction);[3] the decarboxylative alkylation of quinolines with *N*-acyloxy-2-thiopyridones, prepared from alkanoic acids and *N*-hydroxy-2-thiopyridone, under irradiation with a tungsten lamp (the Barton decarboxylation);[4] and the introduction of alkyl groups into quinolines with alkyl halides and $(Me_3Si)_3SiH$ or $(Ph_2SiH)_2$ in the presence of AIBN (azobisisobutyronitrile) under warming conditions.[5] These methods are extremely useful, because alkylated quinolines that cannot easily be obtained by ionic electrophilic substitution ($S_EAr$) into quinolines using the Friedel–Crafts alkylation can be smoothly obtained. We have also reported the introduction of ether groups[6a] by heating at 80 °C for 4 h, and amide groups[6b] through irradiation with a mercury lamp at 35–40 °C for 24 h, into quinolines and other electron-deficient heteroaromatic bases using benzoyl peroxide (BPO). On the other hand, only a few methods for the introduction of a hydroxymethyl group into quinolines have been reported. These include the introduction of a hydroxymethyl group into 2-methylquinoline and quinoline with $(NH_4)_2S_2O_8$ in a mixture of methanol and water under reflux conditions;[7a] the thermal or photochemical hydroxymethylation of protonated lepidine with benzoyl peroxide (BPO) in methanol;[7b] the introduction of a hydroxymethyl group into pyridine *N*-oxide with $(NH_4)_2S_2O_8$ in methanol under reflux conditions;[7c] the introduction of a hydroxymethyl group into lepidine, quinoline, and isoquinoline with $(NH_4)_2S_2O_8$, $CF_3CO_2H$, and $AgNO_3$ (cat.) in a mixture of ethylene glycol and water under reflux conditions;[7d] and the introduction of a hydroxymethyl group into quinolines, pyridines, etc., with BPO, $CF_3CO_2H$, and $Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)^{3+}$ [cat.; dtbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl; dF-$CF_3$-ppy = 5-(trifluoromethyl)-2-(2′,4′-difluorophenyl)pyridine] in methanol under irradiation with a blue LED lamp.[7e] Of the various peroxides that have been used for the radical reaction, peroxodisulfates, such as $(NH_4)_2S_2O_8$, $Na_2S_2O_8$, and $K_2S_2O_8$ have become very popular recently; they are inexpensive and stable solids, easy to handle, and effective radical reagents under both transition-metal-mediated[8] and transition-metal-free conditions.[9] Recent reports of their use under transition-metal-mediated conditions include the $(Bu_4N)_4[W_{10}O_{32}]$-catalyzed dehydrogenative coupling of heteroaromatic bases and cycloalkanes with $K_2S_2O_8$ under sunlight-irradiation conditions;[8a] the $AgNO_3$-catalyzed dehydrogenative carbamoylation of pyridines with formamides and $K_2S_2O_8$ in water;[8b] the Ag-salt-catalyzed decarboxylative arylation of arenes and pyridines with arenecarboxylic acids and $K_2S_2O_8$ in acetonitrile;[8c] the $AgNO_3$-catalyzed decarboxylative alkylation and acylation of pyrimidines with $K_2S_2O_8$ in a mixture of dichloromethane and water at room temperature;[8d] and the photoredox-mediated introduction of ether groups into quinolines and isoquinolines with $Na_2S_2O_8$ in the presence of an $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ catalyst in a mixture of acetonitrile and water.[8e] On the other hand, recent reports of their use

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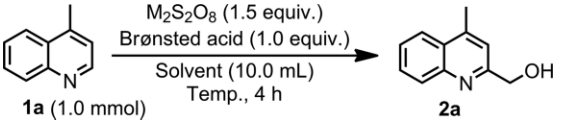
under transition-metal-free conditions include the decarboxylative preparation of fluorenones from *o*-biphenyl-α-ketocarboxylic acids with $Na_2S_2O_8$ in DMSO;[9a] the decarboxylative coupling reaction of α,β-unsaturated carboxylic acids and THF with $K_2S_2O_8$ to form (tetrafuran-2-yl)methyl ketones;[9b] the coupling reaction of phenols to bisphenols with $K_2S_2O_8$;[9c] the remote 4-hydroxylation of piperidinium salts with $K_2S_2O_8$ in water;[9d] the acylation of pyridines with alcohols and $K_2S_2O_8$ in water;[9e] the introduction of ether groups into quinoline, isoquinoline, and pyridine with $K_2S_2O_8$ in a mixture of ether and water;[9f] the introduction of amide groups into benzothiazoles with $K_2S_2O_8$ in tertiary amide;[9g] and the visible-light-promoted introduction of ether groups into quinoline and benzothiazole with $K_2S_2O_8$ in a mixture of ether and water.[9h]

The hydroxymethylation of quinolines with peroxodisulfates in methanol is very attractive, due to the low cost and simplicity of the procedure. However, to the best of our knowledge, no detailed study for the introduction of a hydroxymethyl group into quinolines and isoquinolines has been conducted, and the generality and synthetic utility of hydroxymethylated quinolines remain unknown. Here, we would like to report the introduction of a hydroxymethyl group into quinolines and isoquinolines bearing functional groups with $Na_2S_2O_8$ under warming conditions without use of any transition metals.

## Results and Discussion

A solution of lepidine (**1a**; 1.0 mmol) and a peroxodisulfate (1.5 equiv.) such as $(NH_4)_2S_2O_8$, $K_2S_2O_8$, or $Na_2S_2O_8$, in the presence of $CF_3CO_2H$ (1.0 mmol) in methanol (10.0 mL), was warmed at 80 °C for 4 h to give 2-hydroxymethyl-4-methylquinoline (**2a**) in moderate yields, together with recovered lepidine (Table 1, Entries 1–3). These reactions gave similar yields, but more starting material was recovered in the reaction with $Na_2S_2O_8$ than with the other peroxodisulfates. Therefore, we decided to use $Na_2S_2O_8$ as the oxidant. The addition of water as cosolvent increased the yield of compound **2a** (Table 1, Entries 4–7), and a mixture of methanol and water (7:3) was found to be most suitable (Entry 5). A screening of reaction temperatures revealed that 70 °C was the preferred temperature (Table 1, Entry 8 compared with Entries 5 and 9). Moreover, when the acid was changed to *p*-TsOH·$H_2O$, $CH_3SO_3H$, $CF_3SO_3H$, $H_2SO_4$, or $CH_3CO_2H$ instead of $CF_3CO_2H$, the yield of compound **2a** hardly changed (Table 1, Entries 8 and 10–14). We found that in fact an acid is not required for the reaction of lepidine (**1a**) with $Na_2S_2O_8$; the reaction was carried out with 1.5 equiv. or 2.0 equiv. $Na_2S_2O_8$ (Method A) to give the corresponding product **2a** in 80 % and 86 % yields, respectively (Table 1, Entries 15 and 16). When the reaction was carried out with $Na_2S_2O_8$ (2.0 equiv.) and $CF_3CO_2H$ (1.3 equiv.) (Method B), or with $Na_2S_2O_8$ (2.0 equiv.) and *p*-TsOH·$H_2O$ (1.3 equiv.) (Method C), the yield of compound **2a** increased slightly to 91 % and 90 %, respectively (Table 1, Entries 19 and 20). When $(NH_4)_2S_2O_8$ was used instead of $Na_2S_2O_8$ under the same conditions, the yield of compound **2a** decreased slightly to 87 % and 88 %, respectively (Table 1, Entries 21 and 22). When the reaction was carried out under irradiation with a mercury lamp (400 W, high pressure) at 35–40 °C for 24 h, the yield of compound **2a** dropped to 59 % (Table 1, Entry 17). On the other hand, when the reaction was carried out in either a mixture of ethanol and water (7:3), a mixture of propanol and water (7:3), or a mixture of 2-propanol and water (7:3), instead of the usual mixture of methanol and water (7:3), both in the absence and presence of $CF_3CO_2H$, using the same procedure and under the same conditions, 2-[1′-(hydroxy)ethyl]-4-methylquinoline, 2-[1′-(hydroxy)propyl]-4-methylquinoline, and 2-[1′-(hydroxy)-1′-(methyl)ethyl]-4-methylquinoline were not obtained at all, and lepidine was quantitatively recovered. Then, gram-scale experiments were carried out with 10.0 mmol of lepidine (**1a**) in the absence of acid (Method A), and in the presence of $CF_3CO_2H$ (Method B) or *p*-TsOH (Method C), using the same procedure and reaction conditions as given in Table 1, Entries 16, 19, and 20; compound **2a** was formed in 81 %, 91 %, and 92 % yields, respectively, as shown in Table 2. Thus, this method can be used for gram-scale synthesis.

Table 1. Optimization for hydroxymethylation of lepidine.

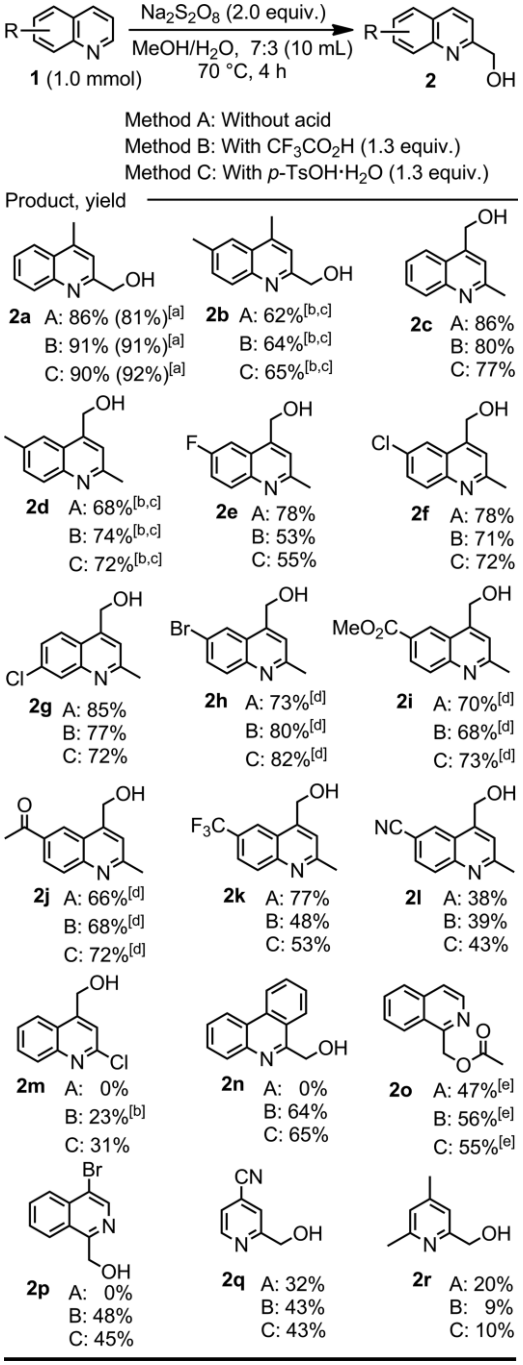



| Entry | $M_2S_2O_8$ | Brønsted acid | Solvent | Temp. [°C] | Yield [%] |
|---|---|---|---|---|---|
| 1 | $(NH_4)_2S_2O_8$ | $CF_3CO_2H$ | MeOH | 80 | 51 (39)[a] |
| 2 | $K_2S_2O_8$ | $CF_3CO_2H$ | MeOH | 80 | 52 (40)[a] |
| 3 | $Na_2S_2O_8$ | $CF_3CO_2H$ | MeOH | 80 | 52 (47)[a] |
| 4 | $Na_2S_2O_8$ | $CF_3CO_2H$ | MeOH/$H_2O$, 8:2 | 80 | 73 (12)[a] |
| 5 | $Na_2S_2O_8$ | $CF_3CO_2H$ | MeOH/$H_2O$, 7:3 | 80 | 85 (3)[a] |
| 6 | $Na_2S_2O_8$ | $CF_3CO_2H$ | MeOH/$H_2O$, 6:4 | 80 | 84 (4)[a] |
| 7 | $Na_2S_2O_8$ | $CF_3CO_2H$ | MeOH/$H_2O$, 5:5 | 80 | 78 (8)[a] |
| 8 | $Na_2S_2O_8$ | $CF_3CO_2H$ | MeOH/$H_2O$, 7:3 | 70 | 88 (4)[a] |
| 9 | $Na_2S_2O_8$ | $CF_3CO_2H$ | MeOH/$H_2O$, 7:3 | 60 | 74 (20)[a] |
| 10 | $Na_2S_2O_8$ | *p*-TsOH·$H_2O$ | MeOH/$H_2O$, 7:3 | 70 | 85 (5)[a] |
| 11 | $Na_2S_2O_8$ | $CH_3SO_3H$ | MeOH/$H_2O$, 7:3 | 70 | 82 (6)[a] |
| 12 | $Na_2S_2O_8$ | $CF_3SO_3H$ | MeOH/$H_2O$, 7:3 | 70 | 81 (7)[a] |
| 13 | $Na_2S_2O_8$ | $H_2SO_4$ | MeOH/$H_2O$, 7:3 | 70 | 74 (16)[a] |
| 14 | $Na_2S_2O_8$ | $CH_3CO_2H$ | MeOH/$H_2O$, 7:3 | 70 | 77 (9)[a] |
| 15 | $Na_2S_2O_8$ | – | MeOH/$H_2O$, 7:3 | 70 | 80 (8)[a] |
| 16 | $Na_2S_2O_8$[c] | – | MeOH/$H_2O$, 7:3 | 70 | 86 |
| 17[b] | $Na_2S_2O_8$[c] | – | MeOH/$H_2O$, 7:3 | 40 | 59 (16)[a] |
| 18 | $Na_2S_2O_8$[c] | $CF_3CO_2H$ | MeOH/$H_2O$, 7:3 | 70 | 88 |
| 19 | $Na_2S_2O_8$[c] | $CF_3CO_2H$[d] | MeOH/$H_2O$, 7:3 | 70 | 91 |
| 20 | $Na_2S_2O_8$[c] | *p*-TsOH·$H_2O$[d] | MeOH/$H_2O$, 7:3 | 70 | 90 |
| 21 | $(NH_4)_2S_2O_8$[c] | $CF_3CO_2H$[d] | MeOH/$H_2O$, 7:3 | 70 | 87 |
| 22 | $(NH_4)_2S_2O_8$[c] | *p*-TsOH·$H_2O$[d] | MeOH/$H_2O$, 7:3 | 70 | 88 |

[a] Yield of recovered lepidine. [b] Reaction was carried out under irradiation with a mercury lamp for 24 h. [c] $Na_2S_2O_8$ (2.0 equiv.) or $(NH_4)_2S_2O_8$ (2.0 equiv.) was used. [d] Brønsted Acid (1.3 equiv.) was used.

Next, the scope of the reaction for the introduction of a hydroxymethyl group into quinoline derivatives **1** (1.0 mmol) using $Na_2S_2O_8$ (2.0 equiv.) was examined. Reactions were carried out in the absence (Method A) or presence of acid (1.3 equiv.; Method B: $CF_3CO_2H$; Method C: *p*-TsOH·$H_2O$) in a mixture of methanol and water (10.0 mL, 7:3) at 70 °C for 4 h (Table 2). Various quinoline derivatives, including 4,6-dimethylquinoline (**1b**), 2-methylquinoline (**1c**), 2,6-dimethylquinoline

Table 2. Hydroxymethylation of quinolines.



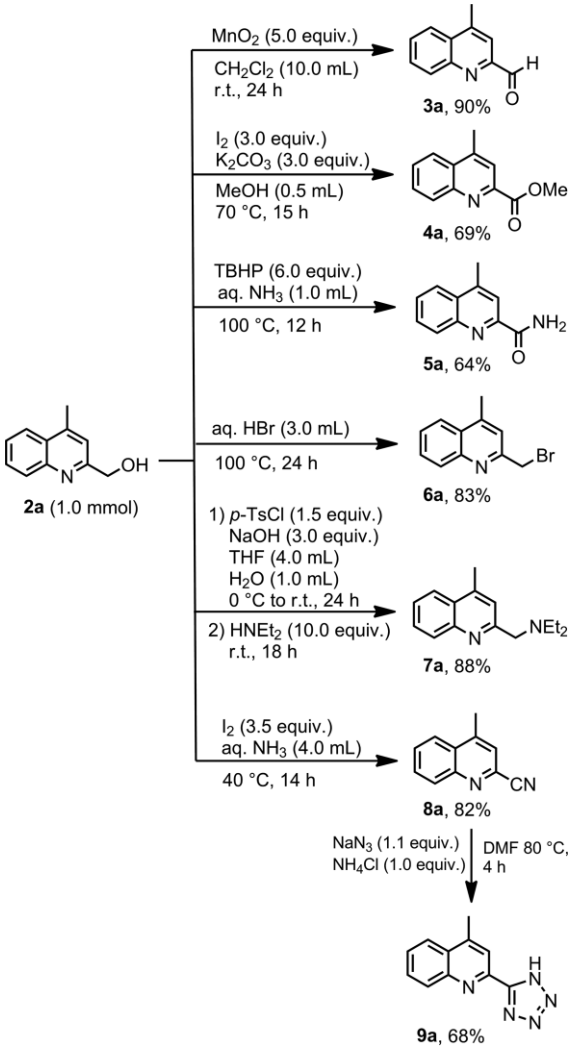

[a] Reaction was carried out on a 10.0 mmol scale. [b] $Na_2S_2O_8$ (3.0 equiv.) was used. [c] Reaction was carried out at 80 °C. [d] $Na_2S_2O_8$ (2.5 equiv.) was used. [e] The OH group of the product was acetylated with $Ac_2O$ after the reaction.

(**1d**), 6-fluoro-2-methylquinoline (**1e**), 6-chloro-2-methylquinoline (**1f**), 7-chloro-2-methylquinoline (**1g**), and 6-bromo-2-methylquinoline (**1h**), were treated with $Na_2S_2O_8$ in the absence of acid, in the presence of $CF_3CO_2H$ (1.3 equiv.), or in the presence of *p*-TsOH·$H_2O$ (1.3 equiv.), in a mixture of methanol and water, and the corresponding quinoline derivatives **2b**–**2h** bearing a hydroxymethyl group were obtained in good to moderate yields (Table 2). In the reactions with quinolines **1b**–**1h**, the yields of products **2** obtained by Methods A, B, and C did not differ markedly from the yields obtained with lepidine (**1a**). When quinoline derivatives **1i**–**1k**, bearing an ester, an acetyl group, and a trifluoromethyl group, were treated with $Na_2S_2O_8$ in a mixture of methanol and water under the same reaction conditions, compounds **2i**–**2k** were produced in good to moderate yields. However, similar treatment of 6-cyano-2-methylquinoline (**1l**) and 2-chloroquinoline (**1m**) with $Na_2S_2O_8$ in the absence or presence of acid generated hydroxymethylated quinolines **2l** and **2m** in low yields. On the other hand, although the same treatment of phenanthridine with $Na_2S_2O_8$ in the absence of acid did not provide hydroxymethylated product **2n** at all, compound **2n** was obtained in 64 % and 65 % yields in the presence of $CF_3CO_2H$ (Method B) and *p*-TsOH·$H_2O$ (Method C), respectively. For isoquinolines, the same treatment of isoquinoline (**1o**) with $Na_2S_2O_8$ in the absence and presence of acid gave 1-(hydroxymethyl)isoquinoline in moderate yields, respectively. However, this slowly decomposed into quinoline and formaldehyde during isolation, probably by an $E_i$ reaction mechanism. Therefore, after the reaction of isoquinoline (**1o**), the solvent was removed, and the residue was treated with $Ac_2O$ to give 1-(acetoxymethyl)isoquinoline (**2o**) in moderate yields in the absence (Method A) and presence of acid (Methods B and C), respectively.

Although the treatment of 4-bromoisoquinoline, which has an electron-withdrawing group, with $Na_2S_2O_8$ in the absence of acid did not provide 4-bromo-1-(hydroxymethyl)isoquinoline (**2p**) at all, compound **2p** was obtained in moderate yields in the presence of $CF_3CO_2H$ (Method B) or *p*-TsOH·$H_2O$ (Method C), without decomposition. On the other hand, the reactivity of pyridines in this method was quite low. For example, the same treatment of 4-cyanopyridine (**1q**), which has two identical electrophilic reaction sites, and 2,4-dimethylpyridine (**1r**) gave 4-cyano-2-hydroxymethylpyridine (**2q**) and 2-hydroxymethyl-4,6-dimethylpyridine (**2r**), respectively, in low yields in the absence or presence of acid.

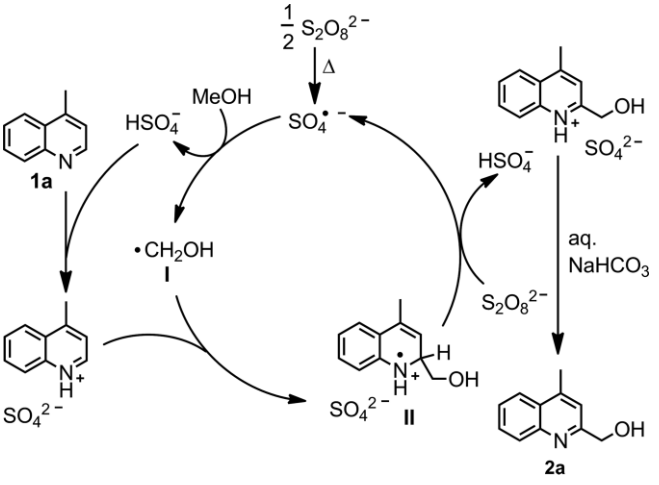
Next, functionalization of the hydroxymethyl group in 2-hydroxymethyl-4-methylquinoline (**2a**) was carried out, as shown in Scheme 1. Oxidation of the hydroxymethyl group into an aldehyde group with $MnO_2$ in dichloromethane was carried out to give 4-methylquinoline-2-carboxaldehyde (**3a**) in 90 % yield. Oxidative conversion of the hydroxymethyl group into a methyl ester group with $I_2$ and $K_2CO_3$ in methanol[10a] was also carried out to give 2-(methoxycarbonyl)-4-methylquinoline (**4a**) in 69 % yield. Oxidative conversion of the hydroxymethyl group into a primary amide group with TBHP (*tert*-butyl hydroperoxide) and aq. $NH_3$[10b] was carried out to give 4-methylquinoline-2-carboxamide (**5a**) in 64 % yield. Bromination of the hydroxy group with aq. HBr was carried out to give 2-bromomethyl-4-methylquinoline (**6a**) in 83 % yield. Amination of the hydroxy group by reaction with *p*-TsCl and NaOH, and subsequent reaction with diethylamine gave 2-(*N*,*N*-diethylamino)methyl-4-methylquinoline (**7a**) in 88 % yield. Moreover, oxidative conversion of the hydroxymethyl group into a cyano group with $I_2$ and aq. $NH_3$[10c] was carried out to give 2-cyano-4-methylquinoline (**8a**) in 82 % yield. Treatment of the resulting 2-cyano-4-

methylquinoline (**8a**) with $NaN_3$ in DMF provided 4-methyl-2-(tetrazol-5′-yl)quinoline (**9a**) in 68 % yield.




Scheme 1. Functionalization of the hydroxymethyl group in 2-hydroxymethyl-4-methylquinoline (**2a**).

To support the idea of a radical-mediated reaction mechanism, the following experiment was carried out. The reaction of lepidine (**1a**) with $Na_2S_2O_8$ (2.0 equiv.) in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl radical (TEMPO; 1.0 equiv.) without $CF_3CO_2H$ (Method A) or with $CF_3CO_2H$ (Method B) in a mixture of methanol and water (7:3) was carried out at 70 °C for 4 h; C–C-bonded compound **2a** was not obtained at all, and lepidine (**1a**) was recovered in 90 % and 88 % yields, respectively. This suggests that the reaction proceeds by a radical mechanism. A plausible reaction pathway is shown in Scheme 2 with lepidine (**1a**). An $SO_4^{\bullet-}$ species formed by the homolytic bond cleavage of $S_2O_8^{2-}$ under warming conditions abstracts an α hydrogen atom from the methyl group of methanol to form carbon-centered hydroxymethyl radical **I** and $HSO_4^-$. This nucleophilic carbon-centered hydroxymethyl radical **I** reacts at the most electrophilic position of protonated lepidine, i.e., the 2-position, to form C–C bonded intermediate **II**. This then reacts further with $S_2O_8^{2-}$ to give a protonated C–C bonded quinoline derivative, together with the generation of $HSO_4^-$ and $SO_4^{\bullet-}$. Quinoline derivative **2a** is obtained by neutralization with satd. aq. $NaHCO_3$ solution.




Scheme 2. Possible reaction mechanism with lepidine.

## Conclusions

The thermal reaction of quinolines and isoquinolines with $Na_2S_2O_8$ in a mixture of methanol and water proceeded smoothly to form hydroxymethylated products in good to moderate yields under transition-metal-free conditions. The addition of acids, such as $CF_3CO_2H$ and *p*-TsOH·$H_2O$, to decrease the electron density on the quinolines and isoquinolines increased the yield of the corresponding hydroxymethylated compounds, depending on the substrate. The introduced hydroxymethyl group was smoothly converted into useful functional groups, such as aldehyde, ester, amide, bromomethyl, aminomethyl, cyano, and tetrazole groups. We believe that this reaction should be useful, as it can be used for the preparation of quinolines and isoquinolines bearing a hydroxymethyl group using a simple and inexpensive inorganic oxidant, i.e., $Na_2S_2O_8$, in a mixture of methanol and water.

## Experimental Section

**General Remarks:** $^1H$ NMR spectra were measured with 400 MHz spectrometers. Data are reported as follows: chemical shift (in ppm on the δ scale relative to internal tetramethylsilane), multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br. = broad), coupling constant [Hz], integration, and assignment. $^{13}C$ NMR spectra were measured at 100 MHz. Chemical shifts are reported in ppm, the solvent resonance was used as an internal standard ($CDCl_3$ at δ = 77.0 ppm). Characteristic peaks in the infrared (IR) spectra are reported in wavenumbers ($cm^{-1}$). High-resolution mass spectra were recorded with Thermo Fisher Scientific Exactive Orbitrap mass spectrometers. Thin-layer chromatography (TLC) was carried out using 0.25 mm silica gel plates (60 $F_{254}$). Products were purified by column chromatography on silica gel 60N (63–210 mesh; spherical, neutral).

**General Procedure for the Reaction of Quinolines 1 with $Na_2S_2O_8$ in a Mixture of Methanol and Water without Acid**

**(Method A):** $Na_2S_2O_8$ (2.0 mmol, 476.2 mg) was added to a solution of lepidine (**1a**; 1.0 mmol, 143.2 mg) in a mixture of methanol and water (7:3; 10.0 mL) in a screw-capped flask (50 mL) at room temperature. The reaction flask was flushed with argon gas. The mixture was stirred for 4 h at 70 °C. The reaction mixture was then cooled to room temperature, and the reaction solvent was removed under reduced pressure. Satd. aq. $NaHCO_3$ solution (10 mL) was added to the residue. The mixture was extracted with EtOAc (3 × 20 mL), and the organic layer was washed with brine (20 mL). The resulting organic layer was dried with $Na_2SO_4$, and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on neutral silica gel (EtOAc/hexane, 1:1) to give the desired product **2a** (148.2 mg, 86 %).

**General Procedure for the Reaction of Quinolines 1 with $Na_2S_2O_8$ and Acid in a Mixture of Methanol and Water (Method B or Method C):** $Na_2S_2O_8$ (2.0 mmol, 476.2 mg) and then $CF_3CO_2H$ (Method B: 1.3 mmol, 0.0995 mL) or *p*-TsOH·$H_2O$ (Method C: 1.3 mmol, 223.9 mg) were added to a solution of lepidine (**1a**; 1.0 mmol, 143.2 mg) in a mixture of methanol and water (7:3; 10.0 mL)in a screw-capped flask (50 mL) at room temperature. The reaction flask was flushed with argon gas. The mixture was stirred for 4 h at 70 °C. The reaction mixture was then cooled to room temperature, and the reaction solvent was removed under reduced pressure. Satd. aq. $NaHCO_3$ solution (10 mL) was added to the residue. The mixture was extracted with $CHCl_3$ (3 × 20 mL), and the organic layer was washed with brine (20 mL). The resulting organic layer was dried with $Na_2SO_4$, and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on neutral silica gel (EtOAc/hexane, 1:1) to give the desired product **2a** (156.8 mg, 91 %).

**2-Hydroxymethyl-4-methylquinoline (2a):** Yellow solid (156.8 mg, 91 %). M.p. 79–80 °C. IR (neat): $\tilde{\nu}$ = 3031, 2793, 1599, 1053, 762 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.70 (s, 3 H), 4.87 (s, 2 H), 7.12 (s, 1 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.71 (t, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 18.7, 64.0, 118.9, 123.7, 126.0, 127.5, 129.0, 129.3, 145.0, 146.4, 158.7 ppm. HRMS (ESI): calcd. for $C_{11}H_{12}NO$ $[M + H]^+$ 174.0913; found 174.0912.

**4,6-Dimethyl-2-hydroxymethylquinoline (2b):** Yellow solid (115.9 mg, 62 %). M.p. 136–137 °C. IR (neat): $\tilde{\nu}$ = 3121, 2909, 1599, 1078, 817 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.57 (s, 3 H), 2.67 (s, 3 H), 4.85 (s, 2 H), 7.08 (s, 1 H), 7.54 (d, *J* = 8.6 Hz, 1 H), 7.73 (s, 1 H), 7.96 (d, *J* = 8.6 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 18.8, 21.8, 63.9, 118.9, 122.8, 127.5, 128.8, 131.5, 135.8, 144.3, 144.9, 157.6 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}NO$ $[M + H]^+$ 188.1070; found 188.1066.

**4-Hydroxymethyl-2-methylquinoline (2c):** White solid (148.8 mg, 86 %). M.p. 145–146 °C. IR (neat): $\tilde{\nu}$ = 3120, 2848, 1604, 1096, 748 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.69 (s, 3 H), 5.19 (s, 2 H), 7.42 (s, 1 H), 7.49 (t, *J* = 8.1 Hz, 1 H), 7.67 (t, *J* = 8.1 Hz, 1 H), 7.88 (d, *J* = 8.1 Hz, 1 H), 8.03 (d, *J* = 8.1 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 25.1, 61.1, 119.0, 122.6, 124.1, 125.8, 128.8, 129.3, 146.5, 147.3, 159.0 ppm. HRMS (ESI): calcd. for $C_{11}H_{12}NO$ $[M + H]^+$ 174.0913; found 174.0912.

**2,6-Dimethyl-4-hydroxymethylquinoline (2d):** Yellow solid (126.8 mg, 68 %). M.p. 149–150 °C. IR (neat): $\tilde{\nu}$ = 3128, 2919, 1373, 1084, 822 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.52 (s, 3 H), 2.67 (s, 3 H), 5.15 (s, 2 H), 7.37 (s, 1 H), 7.49 (d, *J* = 8.6 Hz, 1 H), 7.63 (s, 1 H), 7.92 (d, *J* = 8.6 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 21.7, 24.8, 60.9, 119.0, 121.6, 124.0, 128.2, 131.3, 135.5, 145.6, 146.2, 157.8 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}NO$ $[M + H]^+$ 188.1070; found 188.1066.

**6-Fluoro-4-hydroxymethyl-2-methylquinoline (2e):** White solid (149.2 mg, 78 %). M.p. 161–162 °C. IR (neat): $\tilde{\nu}$ = 3133, 2987, 1165, 1084, 822 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.73 (s, 3 H), 5.12 (s, 2 H), 7.42–7.48 (m, 2 H), 7.52 (dd, *J* = 9.5, 2.7 Hz, 1 H), 8.04 (dd, *J* = 9.5, 5.5 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 25.1, 61.5, 106.6 (d, $J_{C,F}$ = 21.9 Hz), 119.2 (d, $J_{C,F}$ = 24.8 Hz), 119.8, 124.8 (d, $J_{C,F}$ = 9.5 Hz), 131.3 (d, $J_{C,F}$ = 8.6 Hz), 144.6, 145.5 (d, $J_{C,F}$ = 4.8 Hz), 158.3, 160.0 (d, $J_{C,F}$ = 247.0 Hz) ppm. HRMS (ESI): calcd. for $C_{11}H_{11}FNO$ $[M + H]^+$ 192.0819; found 192.0818.

**6-Chloro-4-hydroxymethyl-2-methylquinoline (2f):** White solid (162.1 mg, 78 %). M.p. 159–160 °C. IR (neat): $\tilde{\nu}$ = 3189, 2816, 1603, 1101, 820 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.70 (s, 3 H), 5.13 (s, 2 H), 7.43 (s, 1 H), 7.60 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.87 (d, *J* = 2.4 Hz, 1 H), 7.95 (d, *J* = 8.8 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 25.2, 61.3, 120.0, 121.9, 124.8, 130.1, 130.5, 131.6, 145.3, 145.9, 159.4 ppm. HRMS (ESI): calcd. for $C_{11}H_{11}ClNO$ $[M + H]^+$ 208.0524; found 208.0522.

**7-Chloro-4-hydroxymethyl-2-methylquinoline (2g):** White solid (177.1 mg, 85 %). M.p. 183–184 °C. IR (neat): $\tilde{\nu}$ = 3127, 2837, 1605, 1025, 873 $cm^{-1}$. $^1H$ NMR (400 MHz, $[D_6]$DMSO): $\delta$ = 2.64 (s, 3 H), 4.97 (d, *J* = 4.9 Hz, 2 H), 5.59 (t, *J* = 4.9 Hz, 1 H), 7.47 (s, 1 H), 7.55 (dd, *J* = 8.8, 2.3 Hz, 1 H), 7.95 (d, *J* = 2.3 Hz, 1 H), 8.01 (d, *J* = 8.8 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $[D_6]$DMSO): $\delta$ = 25.0, 59.6, 119.2, 122.6, 125.6, 125.9, 127.3, 133.5, 147.7, 147.9, 160.2 ppm. HRMS (ESI): calcd. for $C_{11}H_{11}ClNO$ $[M + H]^+$ 208.0524; found 208.0523.

**6-Bromo-4-hydroxymethyl-2-methylquinoline (2h):** Yellow solid (180.5 mg, 73 %). M.p. 164–165 °C. IR (neat): $\tilde{\nu}$ = 3186, 2816, 1344, 1101, 818 $cm^{-1}$. $^1H$ NMR (400 MHz, $[D_6]$DMSO): $\delta$ = 2.62 (s, 3 H), 4.94 (d, *J* = 5.2 Hz, 2 H), 5.60 (t, *J* = 5.2 Hz, 1 H), 7.47 (s, 1 H), 7.80 (dd, *J* = 9.1, 2.2 Hz, 1 H), 7.85 (d, *J* = 9.1 Hz, 1 H), 8.18 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $[D_6]$DMSO): $\delta$ = 25.0, 59.7, 118.5, 119.8, 125.4, 125.8, 130.9, 132.0, 145.8, 147.0, 159.4 ppm. HRMS (ESI): calcd. for $C_{11}H_{11}BrNO$ $[M + H]^+$ 252.0019; found 252.0015; calcd. for $[M + H]^+$ 253.9998; found 253.9995.

**4-Hydroxymethyl-6-methoxycarbonyl-2-methylquinoline (2i):** Yellow solid (160.9 mg, 70 %). M.p. 190–192 °C. IR (neat): $\tilde{\nu}$ = 3100, 2826, 1715, 1277, 1044 $cm^{-1}$. $^1H$ NMR (400 MHz, $[D_6]$DMSO): $\delta$ = 2.67 (s, 3 H), 3.91 (s, 3 H), 5.02 (d, *J* = 5.0 Hz, 2 H), 5.65 (t, *J* = 5.0 Hz, 1 H), 7.52 (s, 1 H), 8.00 (d, *J* = 8.6 Hz, 1 H), 8.15 (dd, *J* = 8.6, 1.8 Hz, 1 H), 8.63 (d, *J* = 1.8 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $[D_6]$DMSO): $\delta$ = 25.2, 52.4, 59.8, 120.0, 123.3, 126.1 (2 C), 128.0, 129.3, 148.7, 149.1, 161.5, 166.0 ppm. HRMS (ESI): calcd. for $C_{13}H_{14}NO_3$ $[M + H]^+$ 232.0968; found 232.0966.

**6-Acetyl-4-hydroxymethyl-2-methylquinoline (2j):** Yellow solid (142.3 mg, 66 %). M.p. 179–180 °C. IR (neat): $\tilde{\nu}$ = 3100, 2816, 2838, 1677, 1033, 831 $cm^{-1}$. $^1H$ NMR (400 MHz, $[D_6]$DMSO): $\delta$ = 2.67 (s, 3 H), 2.71 (s, 3 H), 5.08 (d, *J* = 5.0 Hz, 2 H), 5.66 (t, *J* = 5.0 Hz, 1 H), 7.54 (s, 1 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 8.15 (dd, *J* = 8.8, 1.9 Hz, 1 H), 8.59 (d, *J* = 1.9 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $[D_6]$DMSO): $\delta$ = 25.2, 26.9, 59.6, 119.7, 123.2, 125.6, 127.0, 129.2, 133.4, 149.1, 149.3, 161.4, 197.7 ppm. HRMS (ESI): calcd. for $C_{13}H_{14}NO_2$ $[M + H]^+$ 216.1019; found 216.1017.

**4-Hydroxymethyl-2-Methyl-6-(trifluoromethyl)quinoline (2k):** White solid (185.7 mg, 77 %). M.p. 164–165 °C. IR (neat): $\tilde{\nu}$ = 3203, 1613, 1301, 1104, 829 $cm^{-1}$. $^1H$ NMR (400 MHz, $[D_6]$DMSO): $\delta$ = 2.69 (s, 3 H), 5.04 (d, *J* = 5.2 Hz, 2 H), 5.66 (t, *J* = 5.2 Hz, 1 H), 7.57 (s, 1 H), 7.94 (d, *J* = 8.8 Hz, 1 H), 8.11 (d, *J* = 8.8 Hz, 1 H), 8.38 (s, 1 H) ppm. $^{13}C$ NMR (100 MHz, $[D_6]$DMSO): $\delta$ = 25.1, 59.8, 120.4, 121.9 (q, $J_{C,F}$ = 4.8 Hz), 123.3, 124.3 (q, $J_{C,F}$ = 271.8 Hz), 124.4 (q, $J_{C,F}$ = 2.9 Hz), 125.5 (q, $J_{C,F}$ = 31.5 Hz), 130.3, 148.4, 148.7, 161.6 ppm. HRMS (ESI): calcd. for $C_{12}H_{11}F_3NO$ $[M + H]^+$ 242.0787; found 242.0785.

**6-Cyano-4-hydroxymethyl-2-methylquinoline (2l):** Yellow solid (75.0 mg, 38 %). M.p. 208–209 °C. IR (neat): $\tilde{\nu}$ = 3173, 2890, 2228, 1603, 1087 $cm^{-1}$. $^1H$ NMR (400 MHz, [$D_6$]DMSO): $\delta$ = 2.67 (s, 3 H), 5.01 (d, $J$ = 5.2 Hz, 2 H), 5.67 (t, $J$ = 5.2 Hz, 1 H), 7.56 (s, 1 H), 7.96 (dd, $J$ = 8.6, 1.7 Hz, 1 H), 8.03 (d, $J$ = 8.6 Hz, 1 H), 8.57 (d, $J$ = 1.7 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, [$D_6$]DMSO): $\delta$ = 25.3, 59.5, 107.9, 119.0, 120.3, 123.5, 130.0, 130.1, 130.6, 148.3, 148.7, 162.4 ppm. HRMS (ESI): calcd. for $C_{12}H_{11}N_2O$ $[M + H]^+$ 199.0866; found 199.0863.

**2-Chloro-4-(hydroxymethyl)quinoline (2m):** White solid (60.9 mg, 31 %). M.p. 149–150 °C. IR (neat): $\tilde{\nu}$ = 3257, 2923, 2341, 1394, 1146 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.23 (s, 2 H), 7.59 (s, 1 H), 7.59 (td, $J$ = 7.7, 1.3 Hz, 1 H), 7.75 (td, $J$ = 7.7, 1.3 Hz, 1 H), 7.89 (d, $J$ = 8.2 Hz, 1 H), 8.06 (d, $J$ = 8.4 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 61.2, 119.1, 122.7, 124.3, 127.0, 129.2, 130.4, 147.6, 149.5, 151.1 ppm. HRMS (ESI): calcd. for $C_{10}H_9ONCl$ $[M + H]^+$ 194.0367; found 194.0365.

**6-(Hydroxymethyl)phenanthridine (2n):** White solid (129.4 mg, 65 %). M.p. 160–161 °C. IR (neat): $\tilde{\nu}$ = 3356, 2924, 1494, 1239, 863 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.31 (s, 2 H), 7.69–7.74 (m, 3 H), 7.90 (td, $J$ = 7.7, 1.4 Hz, 1 H), 8.00 (d, $J$ = 8.1 Hz, 1 H), 8.17 (dd, $J$ = 8.1, 1.4 Hz, 1 H), 8.58 (dd, $J$ = 8.1, 1.4 Hz, 1 H), 8.67 (dd, $J$ = 8.1 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 61.7, 122.3, 122.8, 123.4, 124.1, 124.2, 127.0, 127.8, 129.0, 129.4, 131.2, 132.9, 142.3, 157.5 ppm. HRMS (ESI): calcd. for $C_{14}H_{12}ON$ $[M + H]^+$ 210.0913; found 210.0913.

**1-(Acetoxymethyl)isoquinoline (2o):** Red oil (112.6 mg, 56 %). IR (neat): $\tilde{\nu}$ = 2960, 1730, 1220, 1142, 921 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.17 (s, 3 H), 5.72 (s, 2 H), 7.63–7.67 (m, 2 H), 7.72 (dt, $J$ = 6.6, 1.1 Hz, 1 H), 7.88 (d, $J$ = 8.2 Hz, 1 H), 8.13 (d, $J$ = 8.2 Hz, 1 H), 8.53 (d, $J$ = 8.2 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 20.8, 65.4, 121.3, 124.5, 126.6, 127.3, 127.6, 130.2, 136.3, 141.8, 154.4, 170.7 ppm. HRMS (ESI): calcd. for $C_{12}H_{12}O_2N$ $[M + H]^+$202.0863; found 202.0859.

**4-Bromo-1-(hydroxymethyl)isoquinoline (2p):** White solid (113.7 mg, 48 %). M.p. 104–105 °C. IR (neat): $\tilde{\nu}$ = 3243, 2360, 1568, 1123, 801 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.22 (s, 2 H), 7.71 (t, $J$ = 7.3 Hz, 1 H), 7.86 (t, $J$ = 7.3 Hz, 1 H), 7.94 (d, $J$ = 8.4 Hz, 1 H), 8.24 (d, $J$ = 8.4 Hz, 1 H), 8.67 (s, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 61.4, 118.9, 123.5, 126.0, 126.8, 128.5, 131.7, 142.1, 148.2, 157.0 ppm. HRMS (ESI): calcd. for $C_{10}H_9ONBr$ $[M + H]^+$237.9862; found 237.9857.

**2-(Hydroxymethyl)isonicotinonitrile (2q):** White solid (57.1 mg, 43 %). M.p. 92–93 °C. IR (neat): $\tilde{\nu}$ = 3377, 3077, 2844, 2238, 1404, 1055 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 3.56 (t, $J$ = 4.9 Hz, 1 H), 4.85 (d, $J$ = 4.9 Hz, 2 H), 7.46 (d, $J$ = 5.1 Hz, 1 H), 7.62 (s, 1 H), 8.75 (d, $J$ = 5.1 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 64.1, 116.4, 121.0, 122.3, 123.7, 149.6, 161.4 ppm. HRMS (ESI): calcd. for $C_7H_7N_2O$ $[M + H]^+$ 135.0553; found 135.0553.

**4,6-Dimethyl-2-(hydroxymethyl)pyridine (2r):** White solid (27.4 mg, 20 %). M.p. 74–75 °C. IR (neat): $\tilde{\nu}$ = 3181, 2917, 2877, 1615, 2829, 1376, 1150, 950, 739 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.31 (s, 3 H), 2.50 (s, 3 H), 4.67 (s, 2 H), 6.86 (s, 1 H), 6.88 (s, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 20.8, 23.8, 63.9, 118.4, 122.8, 148.1, 157.0, 158.3 ppm. HRMS (ESI): calcd. for $C_8H_{12}ON$ $[M + H]^+$ 138.0913; found 138.0912.

**4-Methylquinoline-2-carboxaldehyde (3a):** $MnO_2$ (5.0 mmol, 434.7 mg) was added to a solution of 2-hydroxymethyl-4-methylquinoline (**2a**; 1.0 mmol, 173.2 mg) in dichloromethane (10.0 mL). The mixture was stirred for 24 h at room temperature. The mixture was then filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on neutral silica gel (EtOAc/hexane, 1:2) to give compound **3a** (153.5 mg, 90 %) as a white solid. M.p. 76–77 °C. IR (neat): $\tilde{\nu}$ = 2826, 1704, 1591, 754, 698 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.79 (s, 3 H), 7.72 (td, $J$ = 8.1, 1.1 Hz, 1 H), 7.82 (td, $J$ = 8.1, 1.1 Hz, 1 H), 7.88 (s, 1 H), 8.07 (dd, $J$ = 8.1, 1.1 Hz, 1 H), 8.25 (dd, $J$ = 8.1, 1.1 Hz, 1 H), 10.20 (s, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 18.9, 117.9, 124.0, 128.9, 130.0, 130.1, 131.0, 146.0, 147.7, 152.1, 194.1 ppm. HRMS (ESI): calcd. for $C_{11}H_{10}NO$ $[M + H]^+$ 172.0757; found 172.0754.

**2-Methoxycarbonyl-4-Methylquinoline (4a):** $I_2$ (3.0 mmol, 761.4 mg) and $K_2CO_3$ (3.0 mmol, 414.6 mg) were added to a solution of 2-hydroxymethyl-4-methylquinoline (**2a**; 1.0 mmol, 173.2 mg) in methanol (0.5 mL). The mixture was stirred for 15 h at 70 °C. The reaction mixture was then cooled to room temperature, and quenched with satd. aq. $Na_2SO_3$ solution (10 mL). The mixture was extracted with EtOAc (3 × 20 mL), and the organic layer was washed with brine (20 mL). The resulting organic layer was dried with $Na_2SO_4$, and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on neutral silica gel (EtOAc/hexane, 1:1) to give compound **4a** (138.8 mg, 69 %) as a white solid. M.p. 106–107 °C. IR (neat): $\tilde{\nu}$ = 2951, 1712, 1596, 1245, 752 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.79 (s, 3 H), 4.09 (s, 3 H), 7.68 (td, $J$ = 7.9, 1.1 Hz, 1 H), 7.79 (td, $J$ = 7.9, 1.1 Hz, 1 H), 8.03–8.09 (m, 2 H), 8.31 (dd, $J$ = 7.9, 1.1 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 18.9, 53.2, 121.6, 123.7, 128.3, 129.3, 129.9, 131.3, 146.0, 147.3, 147.4, 166.2 ppm. HRMS (ESI): calcd. for $C_{12}H_{12}NO_2$ $[M + H]^+$ 202.0863; found 202.0860.

**4-Methylquinoline-2-carboxamide (5a):** TBHP (70 % in water, 6.0 mmol, 0.822 mL) was added to a solution of 2-hydroxymethyl-4-methylquinoline (**2a**; 1.0 mmol, 173.2 mg) in aq. $NH_3$ (28 % in water; 1.0 mL). The mixture was stirred for 12 h at 100 °C. The reaction mixture was then cooled to room temperature, and poured into water (10 mL). The mixture was extracted with EtOAc (3 × 20 mL), and the organic layer was washed with brine (20 mL). The resulting organic layer was dried with $Na_2SO_4$, and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on neutral silica gel (EtOAc) to give compound **5a** (119.1 mg, 64 %) as a white solid. M.p. 137–138 °C. IR (neat): $\tilde{\nu}$ = 3435, 3139, 1710, 1669, 1400 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.79 (s, 3 H), 5.69 (br., 1 H), 7.66 (td, $J$ = 8.0, 1.0 Hz, 1 H), 7.77 (td, $J$ = 8.0, 1.0 Hz, 1 H), 8.06 (dd, $J$ = 8.0, 1.0 Hz, 1 H), 8.10 (br., 1 H), 8.11 (dd, $J$ = 8.0, 1.0 Hz, 1 H), 8.16 (s, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 18.9, 119.3, 123.8, 127.8, 129.3, 129.7, 130.4, 146.1, 146.5, 148.8, 167.2 ppm. HRMS (ESI): calcd. for $C_{11}H_{11}N_2O$ $[M + H]^+$ 187.0866; found 187.0863.

**2-(Bromomethyl)-4-methylquinoline (6a):** A solution of 2-hydroxymethyl-4-methylquinoline (**2a**; 1.0 mmol, 173.2 mg) in aq. HBr (47 % in water; 3.0 mL) was stirred for 24 h at 100 °C. The reaction mixture was then cooled to room temperature, and quenched with satd. aq. $NaHCO_3$ solution (30 mL). The mixture was extracted with EtOAc (3 × 30 mL), and the organic layer was washed with brine (50 mL). The resulting organic layer was dried with $Na_2SO_4$, and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on neutral silica gel (EtOAc/hexane, 1:2) to give compound **6a** (195.4 mg, 83 %) as a white solid. M.p. 81–82 °C. IR (neat): $\tilde{\nu}$ = 2922, 1596, 1445, 1189, 766 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.72 (s, 3 H), 4.67 (s, 2 H), 7.41 (s, 1 H), 7.57 (t, $J$ = 8.0 Hz, 1 H), 7.72 (t, $J$ = 8.0 Hz, 1 H), 7.98 (d, $J$ = 8.0 Hz, 1 H), 8.06 (d, $J$ = 8.0 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 18.7, 34.5, 121.6, 123.5, 126.7, 127.3, 129.5, 129.7, 145.6, 147.2, 156.4 ppm. HRMS (ESI): calcd. for $C_{11}H_{11}BrN$ $[M + H]^+$ 236.0069; found 236.0068; calcd. for $[M + H]^+$ 238.0049; found 238.0047.

**Preparation of 2-(*N*,*N*-Diethylamino)methyl-4-methylquinoline (7a):** A solution of *p*-TsCl (1.5 mmol, 286.0 mg) in THF (1.0 mL) was added dropwise to a solution of 2-hydroxymethyl-4-methylquinoline (**2a**; 1.0 mmol, 173.2 mg) and NaOH (3.0 mmol, 120.0 mg) in a mixture of THF and water (3:1; 4.0 mL) at 0 °C. The mixture was stirred for 24 h at room temperature. Then, the reaction mixture was added to diethylamine (1.04 mL). The mixture was stirred for 18 h at room temperature. The reaction mixture was poured into water (10 mL). Then, the mixture was extracted with EtOAc (3 × 20 mL), and the obtained organic layer was dried with $Na_2SO_4$. The mixture was filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on neutral silica gel (EtOAc/methanol, 2:1) to give compound **7a** (200.4 mg, 88 %) as a yellow oil. IR (neat): $\tilde{\nu}$ = 2967, 2807, 1603, 1447, 754 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.08 (t, $J$ = 7.0 Hz, 6 H), 2.63 (q, $J$ = 7.0 Hz, 4 H), 2.70 (s, 3 H), 3.85 (s, 2 H), 7.50–7.56 (m, 2 H), 7.68 (t, $J$ = 8.2 Hz, 1 H), 7.97 (d, $J$ = 8.2 Hz, 1 H), 8.05 (d, $J$ = 8.2 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 11.8, 18.7, 47.5, 60.4, 121.6, 123.6, 125.6, 127.4, 128.9, 129.4, 144.2, 147.3, 161.0 ppm. HRMS (ESI): calcd. for $C_{15}H_{21}N_2$ $[M + H]^+$ 229.1699; found 229.1695.

**2-Cyano-4-methylquinoline (8a):** A solution of 2-hydroxymethyl-4-methylquinoline (**2a**; 1.0 mmol, 173.2 mg) and $I_2$ (3.5 mmol, 888.3 mg) in aq. $NH_3$ (28 % in water; 4.0 mL) was stirred for 14 h at 40 °C. The reaction mixture was cooled to room temperature, and quenched with satd. aq. $Na_2SO_3$ solution (10 mL). The mixture was extracted with EtOAc (3 × 20 mL), and the organic layer was washed with brine (20 mL). The resulting organic layer was dried with $Na_2SO_4$, and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on neutral silica gel (EtOAc/hexane, 1:2) to give compound **8a** (138.1 mg, 82 %) as a white solid. M.p. 94–95 °C. IR (neat): $\tilde{\nu}$ = 3055, 2233, 1588, 856, 770 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.78 (s, 3 H), 7.54 (s, 1 H), 7.72 (td, $J$ = 8.1, 1.0 Hz, 1 H), 7.83 (td, $J$ = 8.1, 1.0 Hz, 1 H), 8.05 (dd, $J$ = 8.1, 1.0 Hz, 1 H), 8.16 (dd, $J$ = 8.1, 1.0 Hz, 1 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 18.7, 117.6, 123.8 (2 C), 128.7, 129.1, 130.5, 130.8, 133.3, 146.6, 147.8 ppm. HRMS (APCI): calcd. for $C_{11}H_9N_2$ $[M + H]^+$ 169.0760; found 169.0757.

**Preparation of 4-Methyl-2-(tetrazol-5′-yl)quinoline (9a):** A solution of 2-cyano-4-methylquinoline (**8a**; 2.0 mmol, 336.4 mg), $NaN_3$ (2.2 mmol, 143.1 mg), and $NH_4Cl$ (2.0 mmol, 107.0 mg) in DMF (2.0 mL) was stirred for 4 h at 80 °C. Then, the reaction mixture was concentrated to dryness. The residue was purified by column chromatography on neutral silica gel (EtOAc/ethanol, 3:1) to give compound **9a** (285.3 mg, 68 %) as a white solid. IR (neat): $\tilde{\nu}$ = 2748, 1651, 1599, 1454, 1241 $cm^{-1}$. $^1H$ NMR (400 MHz, [$D_6$]DMSO): $\delta$ = 2.77 (s, 3 H), 7.70 (td, $J$ = 7.6, 1.1 Hz, 1 H), 7.84 (td, $J$ = 7.6, 1.1 Hz, 1 H), 8.10–8.17 (m, 3 H) ppm. $^{13}C$ NMR (100 MHz, [$D_6$]DMSO): $\delta$ = 18.4, 120.1, 124.6, 127.6, 128.0, 129.4, 130.4, 144.8, 146.7, 147.0, 156.1 ppm. HRMS (ESI): calcd. for $C_{11}H_{10}N_5$ $[M + H]^+$ 212.0931; found 212.0931.

**Supporting Information** (see footnote on the first page of this article): Copies of the $^1H$ and $^{13}C$ NMR spectra of all products **2a**–**2r** and **3a**–**9a**.

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