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Regioselective preparation and NMR spectroscopy study of 2-chloro-4-ethoxy-quinoline for the synthesis of 2-((3-aminopropyl)amino)quinolin-4(1*H*)-one

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Abstract:

Herein, we describe the C4-ethoxylation of 2,4-dichloroquinoline to prepare 2-chloro-4-ethoxy-quinoline (**3**), which is a prominent intermediate used for the synthesis of 2-substituted quinolones. To achieve this goal we studied different conditions for the reaction between 2,4-dichloroquinoline and sodium ethoxide. We discovered that the use of 18-crown-6 ether as an additive and DMF as the reaction solvent allowed us to obtain the desired product **3** in very good yield and selectivity. In addition, a definitive distinction between the C2 and C4 ethoxylation products was achieved using ^{1}H-^{15}N HMBC. Compound **3** is an intermediate used for the synthesis of 2-((3-aminopropyl)amino)quinolin-4(1*H*)-one (**5**), which displays peculiar behavior during ^{1}H NMR analysis, such as the broadening of the H8 singlet and unexpected deuteration at the C8-position. Effort has been dedicated to understand these findings.

Keywords: NMR, ^{1}H-^{15}N HMBC, H/D Exchange, Quinolines, Quinolones, Bederocin.

INTRODUCTION

Quinoline derivatives are useful in a diverse range of applications, including pharmaceuticals, and are present in several drugs including antimalarial (chloroquine, mefloquine, etc.), antibacterial (quinolones and fluoroquinolones), and anticancer (camptothecin, irinotecan, etc.) agents. Among the quinoline derivatives, 2-substituted quinolones are a class of bioactive compounds,[1–5] which include bederocin,[6] an antibacterial compound bearing a 2-aminoalkyl side-chain (Figure 1). The synthesis of 2-substituted quinolones uses 4-alkoxy-2-haloquinolines as the main intermediate (Figure 1), which are versatile substrates and susceptible to nucleophilic attack by nitrogen, sulfur or oxygen nucleophiles at the C2-position.

4-Alkoxy-2-haloquinolines have been prepared using different synthetic pathways, including the one-step monoalkoxy-dehalogenation of 2,4-dihalogenoquinolines,[7] a two-step sequence via alkylation/deoxy-chlorination of 4-hydroxyquinolin-2(1*H*)-one,[3] and three-step route via dialkoxy-dehalogenation/2-dealkoxylation/2-deoxy-chlorination[8] or 2-dechlorination/4-alkoxylation/2-deoxy-chlorination[9] of 2,4-dichloroquinolines. In fact, the simplest strategy used to prepare 4-alkoxy-2-haloquinolines is the one-step monoalkoxy-dehalogenation of 2,4-dihalogenoquinolines, although the regioselectivity of this route has not been well described or studied. In this context, the present work investigates the regioselective alkoxylation of 2,4-dihalogenoquinolines. In addition, we have performed a ^{1}H-^{15}N HMBC study to differentiate between the 2- and 4-substitution products. Despite ^{1}H-^{15}N HMBC being a very useful tool for the structural determination of heterocyclic compounds, alkaloids etc,[10–12] its application to the structural elucidation of quinoline derivatives has not been widely explored, however, some examples include Au (III) chloride compounds with 7,8-benzoquinoline, natural products, and indolo[2,3*b*]quinolines.[13–16]

RESULTS AND DISCUSSION

Despite the regioselective monoalkoxy-dehalogenation of 2,4-dihalogenoquinolines being well established to furnish exclusively 2-alkoxy-4-halogenoquinolines,[17] there are no studies concerning the optimization of the reaction conditions for the selective formation of their 4-alkoxy-2-halogenoquinoline isomers. Therefore, we decided to study the regioselective synthesis of 4-ethoxy-2-chloroquinoline **3**, which can be used as an intermediate in the synthesis of 2-substituted quinolones.[4] Compound **3** can be obtained by the aromatic nucleophilic substitution of 2,4-dichloroquinoline **1** using sodium ethoxide.

However, this reaction can lead to the formation of the 2- or 4-subsitution products, and the yield and isomeric ratio of **2** and **3** are heavily influenced by reaction conditions (Table 1).

Initially, aiming for the regioselective synthesis of **3**, we were inspired by the work of Jarvest et al.,[7] who introduced the use of 15-crown-5 to increase the selectivity in the synthesis of 4-benzyloxy-2-chloro-quinoline, however, the reaction conditions, reagent stoichiometry, or yield were not reported. The addition of crown ether was used to increase the amount of 4-substitution by reducing the postulated complexation of sodium by the quinoline nitrogen atom, which favors substitution at the 2-position.[17] Under these conditions, the crown ether increased the ratio of 4-substitution to 2-substitution from 1:7 to 1:1. That being so, we chose to use 15-crown-5 in our initial tests (entries 1 and 2). Using 20 mol% of crown ether in THF at 50 °C, a mixture of **2** and **3** was obtained in 83% yield, but only a slight excess of the isomer of interest **3** was formed. The consumption of starting material was monitored by TLC and the isomers were easily separated by column chromatography. When the amount of crown ether was reduced to 10 mol%, there was a decrease in the yield and selectivity. An increase in the selectivity was observed using 18-crown-6 (20 mol%) (entry 3), although with no significant increase in yield when compared to 15-crown-5 (entry 1). No improvement in terms of yield or selectivity was observed upon increasing the amount of 18-crown-6 to 50 mol% (entry 4). In the absence of this additive, there was a complete change in the selectivity with the C2-substitution product favored in an 88:12 (**2**:**3**) ratio (entry 5). When hexamethylphosphoramide (HMPA, that selectively solvates cations) was used as an alternative additive no selectivity was observed for any of the isomers (entry 6). The solvent effect on the reaction yield and selectivity was also studied. Using toluene, an apolar solvent, we obtained a very slight selectivity on favour of **2**, the undesired isomer (entry 7). Using 1,4-dioxane, an aprotic solvent less polar than THF, a decrease in the reaction yield and considerable loss of selectivity was observed (entry 8 compared to entry 3). However, the use of acetonitrile, DMSO and ethanol, which are notably more polar than THF, resulted in an improved yield of **3**. Unexpectedly, in DMSO the time demanded to the complete consumption of the starting material was longer (entry 10). In an attempt to further improve the selectivity in ethanol, the reaction was performed at ambient temperature: a slight difference in the selectivity was observed, but the yield was slightly decreased and a much longer reaction time was required for full substrate consumption (entry 12). For our delight, when DMF was used as the solvent in the presence of 18-crown-6 as the

additive, both yield and selectivity for **3** were greatly improved (entry 13). A reasonable explanation for this better result could be done by taking into account the theoretical analysis on de-solvation of some cations to organic electrolyte solvents by Okoshi *et al*, which showed a greater de-solvation energy of sodium to amides when compared to mono-nitriles, DMSO and ethers, meaning DMF can solvate sodium more efficiently.[18] Also, we observed a good selectivity in favour of **3** even in the absence of crown ether (entry 14), despite the result being inferior to that using the additive. Our attempts to decrease the reaction time and/or to increase the yield by increasing the temperature[19] did not succeed (entry 15 compared to entry 14). As aforementioned, the addition of crown ether is used to increase the amount of 4-substitution by reducing the postulated complexation between sodium and quinoline nitrogen. Pursuing an alternative manner to avoid the presence of sodium in the reaction medium to avoid the need for crown ether, we proposed to perform the reaction in the absence of sodium ethoxide, expecting the ethanol itself would act as a nucleophile. We planned to improve the reaction kinetic by adding *N,N*-dimethyl-aminopyridine (DMAP) to attack C-4 position providing a better leaving group (the corresponding ammonium cation bonded), however no reaction was observed and the 2,4-dichloroquinoline was recovered (entry 16). In this test, triethylamine was used to prevent substrate protonation by HCl byproduct, since nitrogen protonation would improve attack to C2-position. Although 4-alkoxy-quinolines were preferentially formed in the presence of K_2CO_3 as an additive,[20] we did not have any success when trying to reproduce this protocol using 2,4-dicloroquinoline and sodium ethoxide. When the reaction was performed employing K_2CO_3 as additive in DMF or acetonitrile, the results (entries 17–18) were not satisfactory when compared to that obtained using crown ether in DMF (entry 13).

Considering the possibility of obtaining the 2- and 4-substitution products, we decided to carry out a NMR study[17] that successfully allows them to be definitively distinguished from one another. Although compounds **2** and **3** exhibit different ^{1}H NMR chemical shifts (δ) corresponding to H3 (δ = 7.02 and 6.71 ppm, respectively), this was not enough to accurately correlate each structure with their spectra. Therefore, we employed ^{1}H-^{15}N HMBC to obtain the ^4J correlation between the aliphatic hydrogen (H3) and quinolinic nitrogen (N1) atoms, which can only occur in compound **2**. In order to detect $^4J_{H3\text{-}N1}$, we performed experiments to assess the optimal parameters for the analysis, evaluating the coupling constant *J* (0.5, 2.0, and 5.0 Hz) and spectral width (–300–0, 0–200, and 200–600 ppm). The best analysis conditions were *J* = 2.0 Hz and a spectral window between –300–0 ppm, in which a signal at (5, –50 ppm) appears in the sample containing the 2-ethoxy-substituted isomer **2** (Figure 2).

When the analysis was repeated with a sample containing the 4-ethoxy-substituted isomer **3**, this signal was not detected (Figure 3), as expected, thereby enabling the full spectroscopic elucidation of **2** and **3**.

With the isomer of interest **3** in hand, the next step was the nucleophilic substitution at C2 using an excess of 1,3-propanediamine to give intermediate **4** in 78% yield after purification by column chromatography (Scheme 1). Finally, hydrolysis of **4** in an acidic medium under heating lead to the formation of **5**, which presents the quinolone scaffold bearing an amino-alkyl chain, which is susceptible to subsequent functionalization, such as a reductive amination reaction with a variety of aldehydes.[4,7]

Despite the fact that several bioactive pharmacophores contain moiety **5**, its spectroscopic characterization is still vague. While Jarvest *et al*. reported the H8 signal as a multiplet,[4] in our ^{1}H NMR analysis of **5**, we obtained the H8 signal as a broad singlet, which is unexpected for this kind of aromatic nuclei (Figure 4). The assignment for this signal was confirmed using several other experiments including ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, and ^{1}H-^{13}C HMBC (see Supporting Information).

We studied the effect of diluting the NMR sample in order to evaluate whether the cause of this unusual broadening of H8 signal was due to intermolecular or intramolecular interactions, as shown in Figure 5. We observed that when the NMR sample solution was diluted, the H8 signal shape became a distorted doublet or multiplet. All the hydrogen atom chemical shifts were significantly altered upon diluting the sample concentration from 154 to 77 nM, but were maintained in upon further dilution. These observations indicate the existence of pi-stacking interactions, in which supramolecular aggregates are favored in the concentrated sample solution, which affect the aromatic hydrogen atom signals, as reported by Turcu and Bogdan for the self-association of ciprofloxacin – a quinolone derivative.[21]

We also investigated the temperature effect over the H8 broad signal, and verified its splitting at about 35^{o}C – the coalescence temperature (Figure 6). These findings could indicate the rupture of pi-stacking interactions as a consequence of increasing the temperature, in which supramolecular aggregates are less favored, as also observed on the dilution effect.

As shown in Figure 7, ^{1}H-^{1}H ROESY analysis further confirmed these interactions because several spatial correlations associated with intermolecular interactions were detected, notably the correlations between the propyl chain aliphatic hydrogen atoms (H9, H10, and H11) and aromatic hydrogen atoms (H5, H6, H7, and H8), which are distant from one another in the molecule.

Interestingly, we also observed a reduced integral value for the H3 and H8 signals in **5,** which may indicate hydrogen-deuterium exchange promoted by the deuterated solvent. In order to confirm this reaction, we performed ^{2}H NMR analysis and it was possible to note that deuteration occurred at H1 and H9, as expected, which are labile hydrogens bonded to nitrogen atoms (Figure 8). Furthermore, we observed a not so expected D-H exchange at C3, which has been previously reported by Kurasawa *et al*. for 2-substituted-4-quinolones in acidic media.[22] Inspired by the mechanism postulated in this work, we propose the D-H exchange proceeds via the formation of *keto*-tautomer **II** during the reaction between its enol form and methanol-d_4 (Scheme 2).

However, the ^{2}H NMR spectrum of **5** also shows unexpected deuteration at C8. As depicted in Scheme 3, we propose this exchange takes place through the unfavored formation of **IV**, which is generated by nucleophilic attack of the π-system by deuterated methanol, which causes a disruption in the aromaticity of the benzene ring. The following step involves the removal of D from **IV** by the base available in the reaction, which restores the aromaticity to form **V**. This proposed mechanism can explain the higher degree of deuteration at C8 when compared to C3, N1, or N9, since the formation of **IV** is very slow because of the disruption to its aromaticity and the removal of H being faster than the removal of D. This causes an accumulation of C8-deuterated species, something that does not occur at C3, N1, and N9, because all the steps involved toward deuteration at these positions occur via tautomerization and will require less activation energy.

CONCLUSIONS

In summary, we have reported a regioselective synthesis of 2-chloro-4-ethoxy-quinoline (**3**) starting from 2,4-dichloroquinoline using a simple and efficient protocol. This quinoline

derivative was efficiently distinguished from its regioisomer **2** using ^{1}H-^{15}N HMBC. Furthermore, the desired product 2-((3-aminopropyl)amino)quinolin-4(1*H*)-one (**5**) was studied using NMR spectroscopy and some questions aroused from the spectra data, such as the broadening of the H8 singlet and unexpected deuteration at C8 position. In this context, we dedicated efforts to postulate some reasonable explanations for the peculiar behavior shown by **5**.

EXPERIMENTAL

Materials

2,4-Dichloroquinoline was prepared according a literature procedure.[23] Sodium ethoxide and 1,3-propanediamine were purchased from Sigma Aldrich and used as received without further purification. All reactions were performed under anhydrous conditions, unless stated otherwise. All the solvents were dried overnight over 3 A molecular sieves prior to use.[24] Column chromatography was performed with 70-230 mesh SiO_2. Thin layer chromatography (TLC) was performed using supported silica gel GF254, 0.25 mm thickness. For visualization, TLC plates were placed under UV light 254 nm or ninhydrin solution. All other reagents were purchased at common chemical suppliers and used as received.

Spectra

All NMR experiments were performed on a Bruker Avance IIIHD 400 spectrometer equipped with a BBO 5 mm probe with z-gradient operating at 400.06 MHz for ^{1}H, and 100.46 MHz for ^{13}C. Spectra were taken at 298 K under typical conditions for ^{1}H (spectral width of 6400 Hz with 32 K data points and zero filled to 128 K to give a digital resolution of 0.05 Hz/pt). The 2D-ROSEY experiment used a pre-scan delay of 2.0 s and 256 F1 increments and 4096 data points in the acquisition dimension. Data were processed using a zero-filling up to 512 and a sine window was applied in both *F1* and *F2* dimensions prior to Fourier transformation to given a FID resolution 1.56 Hz. The mixing time (T_m) was 700 ms. Chemical shifts were reported in parts per million (ppm, δ) and referenced to solvents peaks; methanol-d_4 (3.31 ppm) and $CDCl_3$ (7.26 ppm). For the ^{1}H-^{1}H COSY experiments the cosygpqf pulse sequence was used. The resulting two-dimensional data were processed using a QSINE transformation function (implemented in the Topspin3.2 software) in both dimensions prior to Fourier transformation. For the ^{1}H-^{15}N HMBC experiments the hmbcgpndqf pulse sequence was used. Pre-scan delay of 7.0 s. The resulting two-dimensional

data were processed using a SINE transformation function (implemented in the Topspin3.2 software) in both dimensions prior to Fourier transformation. For the ^{1}H-^{13}C HMBC and HSQC experiments the hmbcetgpl3nd and hsqcedetgpsisp2.2 pulses sequences were used, respectively. The resulting two-dimensional data were processed using a QSINE transformation function (implemented in the Topspin3.2 software) in both dimensions prior to Fourier transformation.

Typical procedure for ethoxylation of 2,4-dichloroquinoline

A mixture of 2,4-dichloroquinoline (0.5 mmol, 99.0 mg), sodium ethoxide (0.6 mmol, 52.0 mg), 18-crown-6 (0.1 mmol, 26.5 mg) and DMF (0.5 mL) was stirred at 50ºC for 48 h. After cooling and removal of the volatiles under reduced pressure, the crude material was purified by column chromatography (silica gel, hexane/ethyl acetate) to give compounds **2** (0.024 mmol, 5.0 mg, 5%) and **3** (0.451 mmol, 93.7 mg, 90%) as white solids.

4-chloro-2-ethoxyquinoline (2):

White solid; Yield: 5%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12-8.07 (m, 1H); 7.85-7.81 (m, 1H); 7.66 (ddd, *J* = 8.3; 7.1; 1.3 Hz, 1H); 7.45 (ddd, *J* = 8.2; 7.1; 1.1 Hz, 1H); 7.02 (s, 1H); 4.52 (q, *J* = 7.1 Hz, 1H); 1.44 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.7; 147.2; 143.7; 130.5; 127.7; 124.7; 124.1; 123.4; 113.2; 62.2; 14.6. Rf = 0.70 (5% EtOAc/hexanes).

2-chloro-4-ethoxyquinoline (3):

White solid; Yield: 90%. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.16 (dd, *J* = 8.3; 0.9 Hz, 1H); 7.93 (d, *J* = 8.4 Hz, 1H); 7.70 (ddd, *J* = 8.3; 7.0; 1.3 Hz, 1H); 7.50 (ddd, *J* = 8.4; 7.0; 0.9 Hz, 1H); 6.71 (s, 1H); 4.26 (q, *J* = 7.0 Hz, 2H); 1.58 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.1; 151.7; 148.2; 130.9; 128.1; 126.0; 122.2; 120.5; 101.7; 64.9; 14.5. Rf = 0.33 (5% AcOEt/hexanes).

Preparation of N^1-(4-ethoxyquinolin-2-yl)propane-1,3-diamine (4)

A mixture of 2-chloro-4-ethoxyquinoline **3** (0.3 mmol, 62.0 mg) and 1,3-propanediamine (2.4 mmol, 0.22 mL) was stirred at 70ºC for 48 h. After cooling and removal of the volatiles under reduced pressure, the crude material was purified by column chromatography (silica gel,

dichlorometane/10% ammonium hydroxide in methanolic solution, 94:6) to give compound **4** (0.23 mmol, 56.2 mg) as an yellow solid.

Yellow solid; Yield: 77%. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.90 (dd, *J* = 8.4; 1.4 Hz, 1H); 7.53 (dd, *J* = 8.3; 0.5 Hz, 1H); 7.45 (ddd, *J* = 8.4; 7.0; 1.5 Hz, 1H); 7.12 (ddd, *J* = 8.3; 7.0; 1.4 Hz, 1H); 6.11 (s, 1H); 4.17 (q, *J* = 7.0 Hz, 2H); 3.52 (t, *J* = 6.8 Hz, 2H); 2.77 (t, *J* = 6.8 Hz, 2H); 1.81 (qn, *J* = 6.8 Hz, 2H); 1.51 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (CD_3OD, 400 MHz) δ 163.0; 160.7; 149.7; 130.8; 125.4; 122.7; 122.1; 119.0; 91.4; 65.0; 39.6; 39.3; 33.3; 14.8. Rf = 0.45 (dichlorometane/10% ammonium hydroxide in methanolic solution, 94:6)

Preparation of 2-((3-aminopropyl)amino)quinolin-4(1*H*)-one (5)

A mixture of N^1-(4-ethoxyquinolin-2-yl)propane-1,3-diamine (**4**) (0.2 mmol, 45.0 mg) and concentrated HCl aqueous solution (2.2 mL) was refluxed for 24 h. After cooling, the volatiles were removed under reduced pressure to give compound **5** (0.18 mmol, 54.0 mg) as a pale yellow solid.

Yellow solid; Yield: 90%. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.04 (d, *J* = 7.5 Hz, 1H); 7.89 (s, 1H); 7.74 (ddd, *J* = 8.2; 7.5; 1.1 Hz, 1H); 7.45 (t, *J* = 8.2 Hz, 1H); 6.37 (s, 1H); 3.66 (t, *J* = 6.9 Hz, 2H); 3.15 (t, J = 6.9 Hz, 2H); 2.13 (qn, *J* = 6.9 Hz, 2H). ^{13}C NMR (CD_3OD, 400 MHz) δ 155.89; 155.86; 138.97; 134.08; 125.93; 124.44; 118.48; 117.88; 40.60; 38.28; 27.70. ^{2}H NMR (CD_3OD, 400 MHz) δ 11.97; 8.57; 7.95; 6.38.

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References

[1] Jarvest, R. L.; Berge, J. M.; Brown, P.; Houge-Frydrych, C. S. V.; O'Hanlon, P. J.; McNair, D. J.; Pope, A. J.; Rittenhouse, S. *Bioorganic Med. Chem. Lett.* **2003**, *13*,

1265.

[2] Jarvest, R. L.; Armstrong, S. A.; Berge, J. M.; Brown, P.; Elder, J. S.; Brown, M. J.; Copley, R. C. B.; Forrest, A. K.; Hamprecht, D. W.; O'Hanlon, P. J.; Mitchell, D. J.; Rittenhouse, S.; Witty, D. R. *Bioorganic Med. Chem. Lett.* **2004**, *14*, 3937.

[3] Guo, L. J.; Wei, C. X.; Jia, J. H.; Zhao, L. M.; Quan, Z. S. *Eur. J. Med. Chem.* **2009**, *44*, 954.

[4] Jarvest, R. L.; Berge, J. M.; Berry, V.; Boyd, H. F.; Brown, M. J.; Elder, J. S.; Forrest, A. K.; Fosberry, A. P.; Gentry, D. R.; Hibbs, M. J.; Jaworski, D. D.; O'Hanlon, P. J.; Pope, A. J.; Rittenhouse, S.; Sheppard, R. J.; Slater-Radosti, C.; Worby, A. *J. Med. Chem.* **2002**, *45*, 1959.

[5] Shibata, S.; Gillespie, J. R.; Kelley, A. M.; Napuli, A. J.; Zhang, Z.; Kovzun, K. V.; Pefley, R. M.; Lam, J.; Zucker, F. H.; Van Voorhis, W. C.; Merritt, E. A.; Hol, W. G. J.; Verlinde, C. L. M. J.; Fan, E.; Buckner, F. S. *Antimicrob. Agents Chemother.* **2011**, *55*, 1982.

[6] Green, L. S.; Bullard, J. M.; Ribble, W.; Dean, F.; Ayers, D. F.; Ochsner, U. A.; Janjic, N.; Jarvis, T. C. *Antimicrob. Agents Chemother.* **2009**, *53*, 86.

[7] Jarvest, R. L.; Berge, J. M.; Brown, M. J.; Brown, P.; Elder, J. S.; Forrest, A. K.; Houge-Frydrych, C. S. V.; O'Hanlon, P. J.; McNair, D. J.; Rittenhouse, S.; Sheppard, R. J. *Bioorganic Med. Chem. Lett.* **2003**, *13*, 665.

[8] Ramasamy, A. K.; Balasubramaniam, V.; Mohan, K. *Asian J. Chem.* **2012**, *24*, 4726.

[9] Mahalingam, M.; Mohan, P. S.; Gayathri, K.; Gomathi, R.; Subhapriya, P. *J. Chem. Sci.* **2013**, *125*, 1015.

[10] Köck, M.; Junker, J.; Lindel, T. *Org. Lett.* **1999**, *1*, 2041.

[11] Fort, P. O.; Pinto, D. C. G. a; Santos, C. M. M.; Silva, A. M. S. *Advanced NMR techniques for structural characterization of heterocyclic structures*; 2007; Vol. 661.

[12] Martin, G. E.; Williams, A. J. *Annu. Reports NMR Spectrosc.* **2015**, *84*, 1.

[13] Niedzielska, D.; Pazderski, L.; Wojtczak, A.; Kurzawa, M.; Ścianowski, J.; Szłyk, E. *Polyhedron* **2018**, *139*, 155.

[14] Pearce, A. N.; Chia, E. W.; Berridge, M. V.; Clark, G. R.; Harper, J. L.; Larsen, L.; Maas, E. W.; Page, M. J.; Perry, N. B.; Webb, V. L.; Copp, B. R. *J. Nat. Prod.* **2007**, *70*, 936.

[15] Martin, G. E.; Hadden, C. E. *J. Nat. Prod.* **2000**, *63*, 543.

[16] Bednarek, E.; Sitkowski, J.; Bocian, W.; Łuniewski, W.; Kobylińska, M.; Kaczmarek; Kozerski, L. *Magn. Reson. Chem.* **2013**, *51*, 569.

[17] Osborne, A. G.; Miller, L. A. D. *J. Chem. Soc. Perkin Trans. 1* **1993**, 181.

[18] Okoshi, M.; Yamada, Y.; Yamada, A.; Nakai, H. *J. Electrochem. Soc.* **2013**, *160*, A2160.

[19] Ismail, M. M.; Abass, M.; Hassan, M. M. *Phosphorus. Sulfur. Silicon Relat. Elem.* **2000**, *167*, 275.

[20] Rajesh, K.; Palakshi Reddy, B.; Sarveswari, S.; Vijayakumar, V. *Res. Chem. Intermed.* **2013**, *39*, 4259.

[21] Turcu, I.; Bogdan, M. *J. Phys. Chem. B* **2012**, *116*, 6488.

[22] Kurasawa, Y.; Yoshida, K.; Yamazaki, N.; Sasaki, K.; Zamami, Y.; Min, Z.; Togi, A.; Ito, H.; Kaji, E.; Fukaya, H. *J. Heterocycl. Chem.* **2014**, *51*, 1821.

[23] Naik, M.; Humnabadkar, V.; Tantry, S. J.; Panda, M.; Narayan, A.; Guptha, S.; Panduga, V.; Manjrekar, P.; Jena, L. K.; Koushik, K.; Shanbhag, G.; Jatheendranath, S.; Manjunatha, M. R.; Gorai, G.; Bathula, C.; Rudrapatna, S.; Achar, V.; Sharma, S.; Ambady, A.; Hegde, N.; Mahadevaswamy, J.; Kaur, P.; Sambandamurthy, V. K.; Awasthy, D.; Narayan, C.; Ravishankar, S.; Madhavapeddi, P.; Reddy, J.; Prabhakar, K. R.; Saralaya, R.; Chatterji, M.; Whiteaker, J.; McLaughlin, B.; Chiarelli, L. R.; Riccardi, G.; Pasca, M. R.; Binda, C.; Neres, J.; Dhar, N.; Signorino-Gelo, F.; McKinney, J. D.; Ramachandran, V.; Shandil, R.; Tommasi, R.; Iyer, P. S.; Narayanan, S.; Hosagrahara, V.; Kavanagh, S.; Dinesh, N.; Ghorpade, S. R. *J. Med. Chem.* **2014**, *57*, 5419.

[24] Williams, D. B. G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351.

Figure 1. Quinoline derivatives.

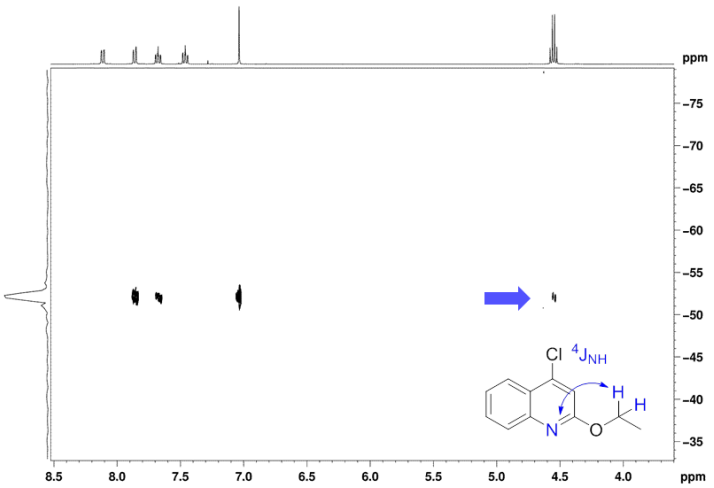


Figure 2. ^1H-^{15}N HMBC contour map of **2** in $CDCl_3$.

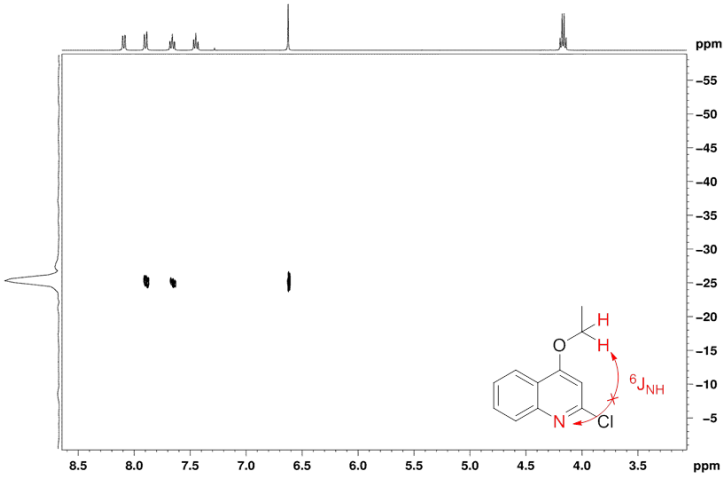


Figure 3. ^1H-^{15}N HMBC contour map of **3** in $CDCl_3$.

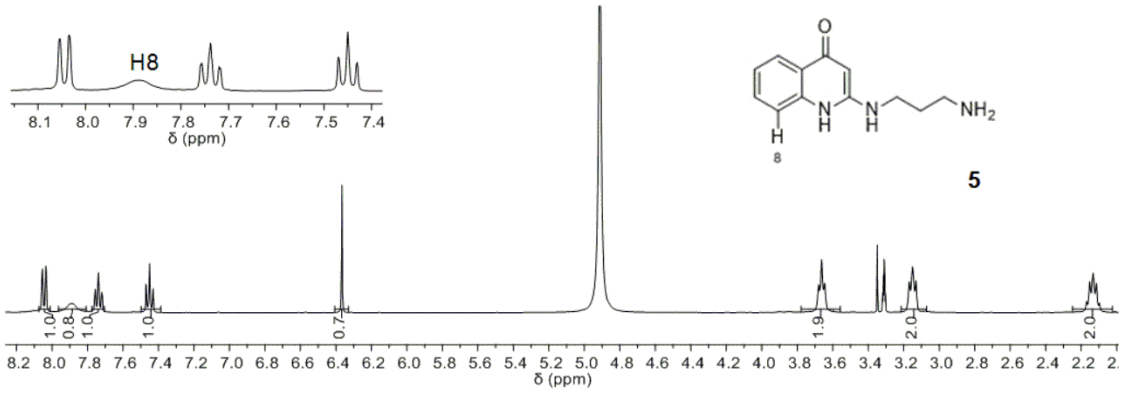


Figure 4. 400 MHz ^{1}H NMR spectrum of **5** recorded in CD_3OD.

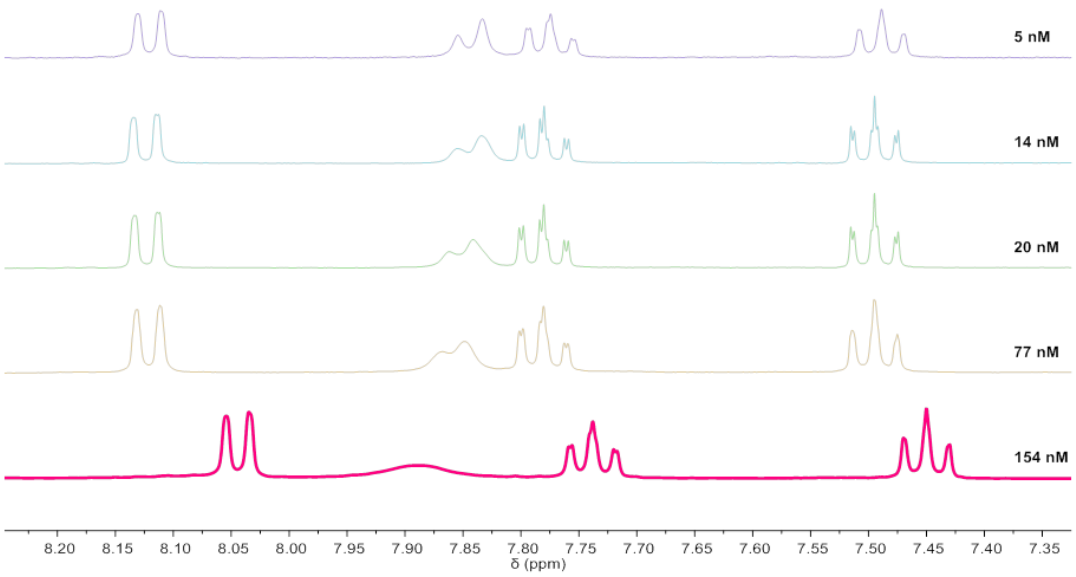


Figure 5. The dilution effect on the signal multiplicity and chemical shifts observed in the ^{1}H NMR spectrum of **5**.

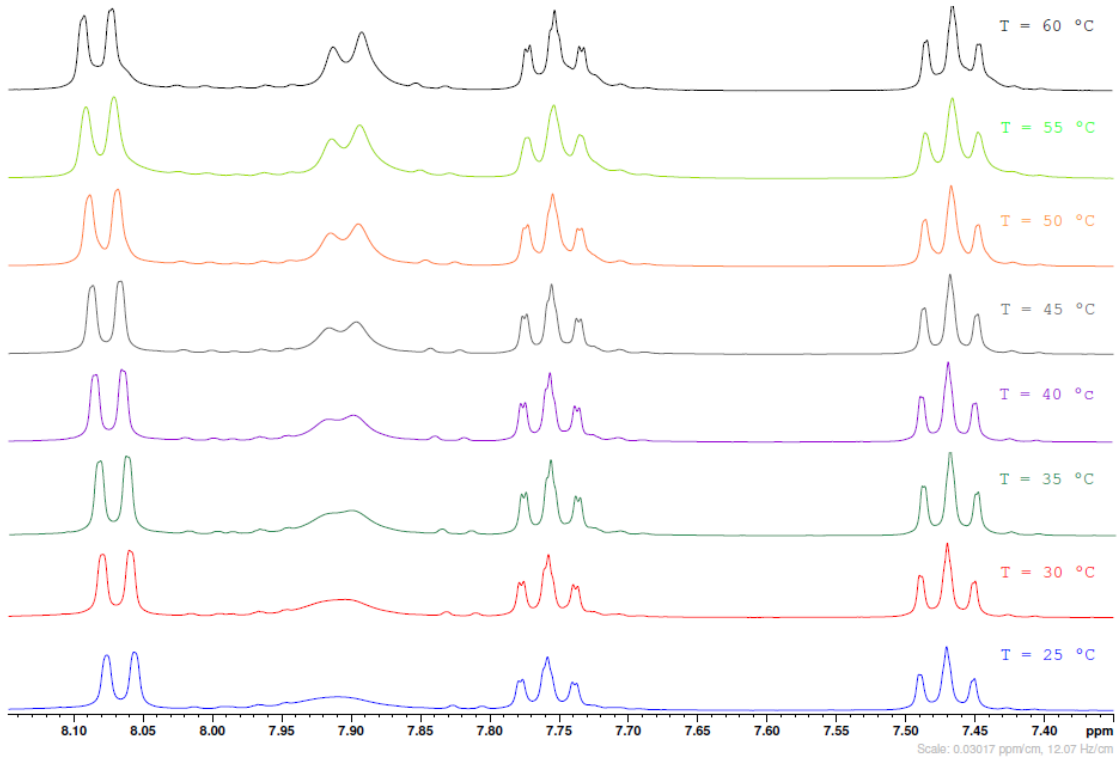


Figure 6. The temperature effect on the H8 signal multiplicity observed in the ^{1}H NMR spectrum of **5**.

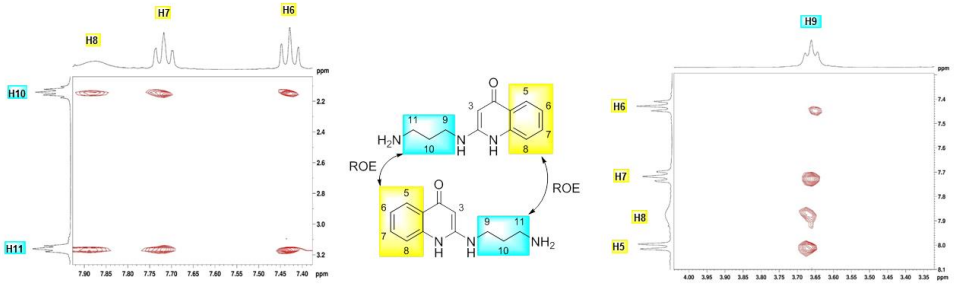


Figure 7. ^{1}H-^{1}H ROESY contour map of **5**.

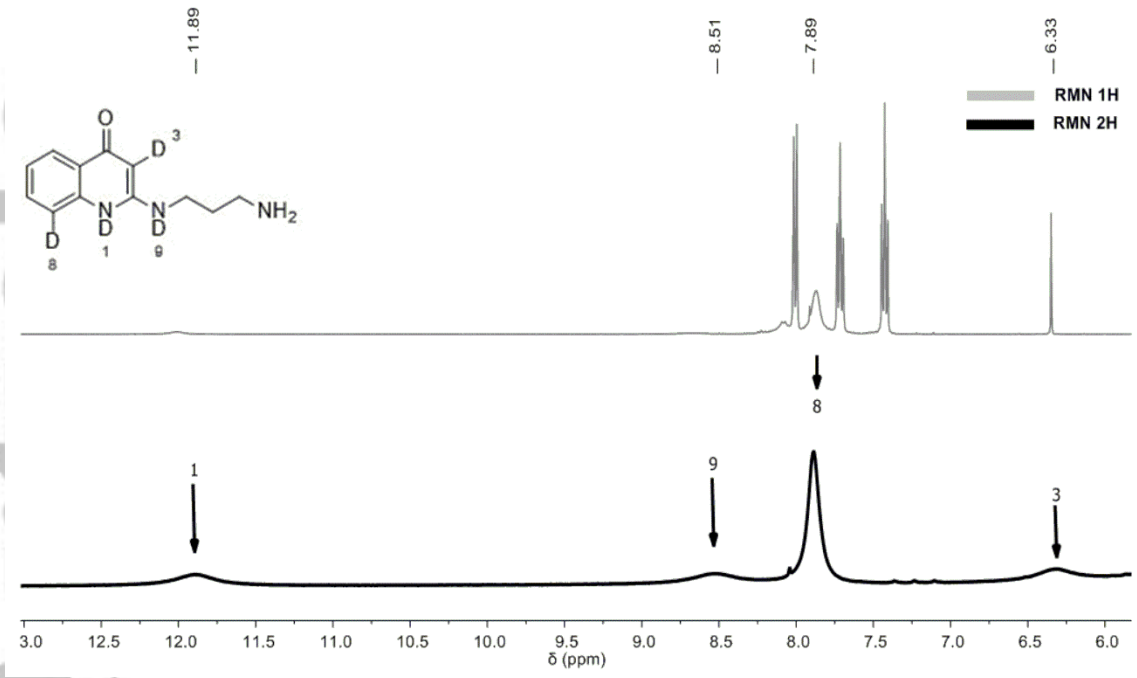
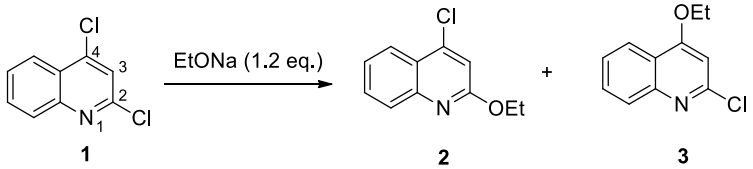


Figure 8. ^{1}H and ^{2}H NMR spectra of **5**.

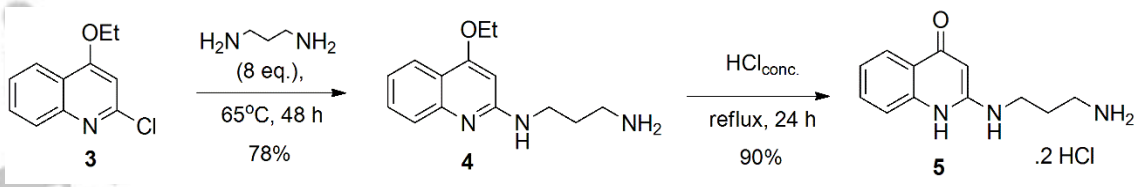
Table 1. The reaction of 2,4-dichloroquinoline and sodium ethoxide under different conditions.



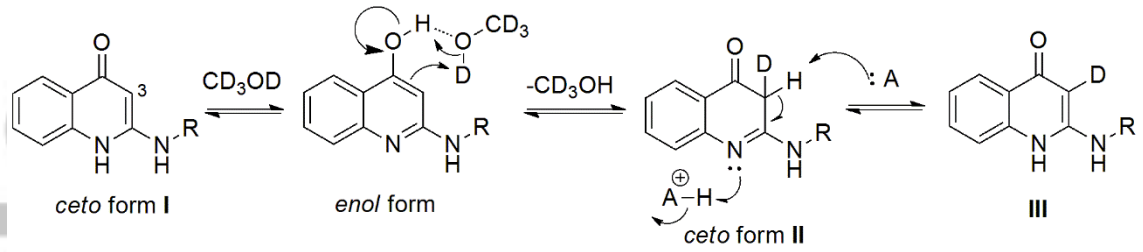
Entry	Additive (mol%)	Reaction time (h)[a]	Solvent	Temp. (°C)	Ratio (2: 3)[b]	Yield (%)[c]
1	15-crown-5 (20)	3	THF	50	42: 58	83
2	15-crown-5 (10)	3	THF	50	44: 56	76
3	18-crown-6 (20)	1	THF	50	34: 66	84
4	18-crown-6 (50)	1	THF	50	31: 69	80
5	-	1	THF	50	88: 12	75
6	HMPA (100)	24	THF	50	50: 50	>95
7	18-crown-6 (20)	2[d]	Toluene	50	55: 45	54
8	18-crown-6 (20)	2	1,4-dioxane	50	47: 53	75
9	18-crown-6 (20)	2	CH_3CN	50	29: 71	69
10	18-crown-6 (20)	72	DMSO	50	33: 67	90
11	18-crown-6 (20)	2	EtOH	50	38: 62	90
12	18-crown-6 (20)	48	EtOH	rt	35: 65	80

13	**18-crown-6 (20)**	**48**	**DMF**	**50**	**15: 85**	**95**
14	-	72[d]	DMF	50	33: 67	65
15	-	48	DMF	reflux	31: 69	67
16[e]	DMAP (10)/ Et_3N (100)	24	EtOH	50	-	0
17	K_2CO_3 (100)	3	DMF	50	29: 71	34
18	K_2CO_3 (100)	3	CH_3CN	50	50: 50	55

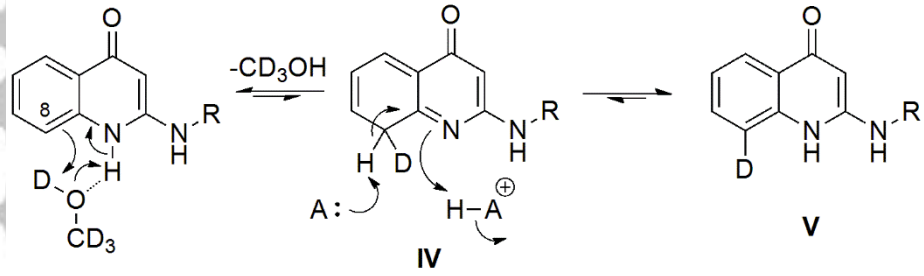
[a]The consumption of 2,4-dichloroquinoline was monitored by TLC. [b]Determined using the ^{1}H NMR spectrum of the crude product from the integral of the peaks observed at δ = 6.99 and 6.67 ppm.[c] The combined isolated yield obtained after purification. [d]This reaction time was considered as maximum [e]The reaction was performed in the absence of EtONa.



Scheme 1. Synthesis of **5** starting from 2-chloro-4-ethoxy-quinoline (**3**).



Scheme 2. The proposed mechanism for deuteration at the C3 position.



Scheme 3. Proposed mechanism for deuteration at the C8 position.