

STUDY ON REACTION OF SUBSTITUTED 4-METHYLQUINOLIN-2(1H)-ONES WITH SODIUM AZIDE

Le The Duan², Nguyen Dinh Thanh^{*,1}, Nguyen Thi Minh Nguyet², Le Thi Hoai², Nguyen Thi Thu Ha²

¹High School for Gifted Students, VNU University of Science (Hanoi, Vietnam)

²Faculty of Chemistry, VNU University of Science

Abstracts. Reaction of different substituted 2-chloro-4-methylquinolines with sodium azide changed the direction to substituted tetrazolo[1,5-a]quinolines instead corresponding 2-azido-4-methylquinolines. Required 2-chloro-derivatives were obtained from substituted 4-methylquinolin-2(1H)-ones, which were synthesized by ring closing corresponding (un)substituted acetoacetanilides in the presence of ionic liquid [Bmim]OH. The structures of obtained compounds have been confirmed by using spectroscopic methods (IR, NMR and MS).

Keywords: Knorr synthesis, 4-methylquinolin-2(1H)-ones, ionic liquid, sodium azido.

1. Introduction

Quinolones present in molecular skeleton of quinolone antibiotics which are currently used in disease treatments [1], and is the most consumed antibacterial quinolone worldwide [2]. Of quinolones quinolin-2(1H)-ones have been synthesized [3], but its 2-chloro derivatives did not study much yet. On the other hand, recently, the ionic liquids have been prepared and study to use in many different chemical processes [4]. Herein, we report some study results about the synthesis and transformations of substituted 4-methylquinolin-2(1H)-ones from corresponding (un)substituted anilines and ethyl acetoacetate.

2. Experimental Section

Melting points were determined by open capillary method on STUART SMP3 instrument (BIBBY STERILIN, UK) and are uncorrected. IR spectra (KBr disc) were recorded on an Impact 410 FT-IR Spectrometer (Nicolet, USA), ¹H and ¹³C NMR spectra were recorded on Avance Spectrometer AV500 (Bruker, Germany) at 500 MHz and 125.8 MHz, respectively, using DMSO-*d*₆ as solvent and TMS as internal standard. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 WF₂₅₄S (Merck, Germany), 1-Butyl-3-methylimidazolium hydroxide, [Bmim]OH, was prepared by our method [5].

2.1. General procedure for synthesis of substituted 4-methylquinolin-2(1H)-ones (3a-h)

To a mixture of appropriate (un)substituted anilines (**1b-d**, 0.1 mol), ethyl acetoacetate (15.1 ml, 0.12 mol) in 100-ml one-necked round-bottomed flask 0.2 ml of [Bmim]OH was added. After that, xylene (15 ml) was added to the reaction mixture with well shaking. A single distillation apparatus was set up and the distillation carried out slowly and carefully for about 120 minutes to remove ethanol was created in reaction. Then, the solvent xylene was removed by rotating distillation under reduced pressure. The residue, namely crude acetoacetanilides **2a-d**, was used directly to ring close to quinoline-2(1H)-ones **3a-d**.

To the above obtained residue in 100-ml one-necked round-bottomed flask 30 ml of 70–72% H₂SO₄ (d=1.72 g/cm³) with well stirring. Then, the reaction mixture was heated

*Corresponding author. Tel.: 84-904204799

Email: nguyendinhthanh@hus.edu.vn

carefully on the water bath at 90°C. The smoke formed at this temperature indicated that the reaction began. After the release of smoke was diminished and the reaction mixture was no longer bubbling gas anymore, the mixture was heated at 95°C for about 30 minutes. Cooled the mixture to about 60°C and poured carefully into 300 g of crushed ice. Filter the precipitate separated, washed well with cold water to pH 7 acid, and crystallize from 96% ethanol to afford products **3a-d** in form of white powder.

2.2. Conversion of quinoline-2(1*H*)-ones **3a-d** into corresponding chloro-derivatives **4a-d**

To appropriate (un)substituted 4-methylquinolin-2(1*H*)-one (**3a** or **3b-d**, 0.02 mol), respectively, in 50-ml one-necked flask freshly distilled phosphoryl chloride (8 ml), shake the mixture well. Heat the reaction mixture on water at 70°C until the solid dissolved completely, then 1 h more. Cooled the reaction mixture to room temperature, and poured slowly and carefully into 300 g of crushed ice while well stirring (noted that crushed ice remained in the mixture to ensure the temperature was not over 20°C in this process), then neutralised the solution with 4M sodium hydroxide to pH 7, and allowed to stand overnight. Checked the pH of the solution, if the pH decreased, then NaOH solution needed to add in order to neutral pH is reached. Filtered the precipitate separated, carefully rinsed with cold water until neutral pH. Crystallized from 96% ethanol to yield products **4a-d** as white powder.

4a, R=H: Opaque white solid, yield 89.2%, mp 51–52°C. IR (KBr) ν (cm⁻¹): 3286, 3057, 2933, 2871, 1581, 1552, 1500, 1439, 1390. ¹H NMR (500.13 MHz, DMSO-*d*₆), δ (ppm): 8.01 (d, 1H, *J* = 8.25 Hz, H-8), 7.96 (d, 1H, *J* = 7.25 Hz, H-5), 7.72 (td, 1H, *J* = 1.0, 7.25 Hz, H-6), 7.58 (td, 1H, *J* = 1.0, 8.25 Hz, H-7), 7.25 (s, 1H, H-3), 2.69 (s, 3H, 4-Me). ¹³C NMR (125.75 MHz, DMSO-*d*₆), δ (ppm): 150.6 (C-2), 147.7 (C-4), 147.6 (C-8a), 130.3 (C-7), 129.2 (C-8), 127.0 (C-4a), 126.7 (C-6), 123.8 (C-5), 122.5 (C-3), 18.6 (4-Me). ESI-MS, *m/z* (%): 180([M+2+H]⁺, 31), 178([M+H]⁺, 100), 183(5), 157(15), 142(15), 120(20), 106(10), 79(20).

4b, R=6-Me: Pale brown solid, yield 96.1%, mp 98–100°C. IR (KBr) ν (cm⁻¹): 3153, 3059, 2915, 2852, 1558, 1501, 1435, 1376. ¹H NMR (500.13 MHz, CDCl₃), δ (ppm): 7.90 (d, 1H, *J* = 8.5 Hz, H-8), 7.71 (pseudo-singlet, 1H, H-5), 7.55 (dd, 1H, *J* = 1.5, 8.5 Hz, H-7), 7.21 (s, 1H, H-3), 2.66 (s, 3H, 6-Me), 2.56 (s, 3H, 4-Me). ¹³C NMR (125.75 MHz, CDCl₃), δ (ppm): 149.6 (C-2), 147.0 (C-4), 146.1 (C-8a), 136.7 (C-6), 132.4 (C-7), 128.8 (C-8), 126.9 (C-4a), 122.9 (C-5), 122.4 (C-3), 21.8 (6-Me), 18.6 (4-Me). ESI-MS, *m/z* (%): 194 ([M+2+H]⁺, 30), 192([M+H]⁺, 100), 179(5), 174(10), 163(10), 157(15), 142(5), 120(5).

4c, R=8-Me: Pale brown solid, yield 86.1%, mp 92–93°C. IR (KBr) ν (cm⁻¹): 3107, 3013, 2956, 2837, 1591, 1426, 1488, 1393.

4d, R=6-OMe: Grey-brown solid, yield 96.2%, mp 130–132°C. IR (KBr) ν (cm⁻¹): 3026, 2930, 2836, 1591, 1563, 1490, 1429, 1390.

2.3. Reaction of

To the mixture consisting of (un)substituted 2-chloro-4-methylquinolin (**4a**, **4b** or **4f**, 1 mmol) and sodium azide (1.5 mmol) in 50 ml of anhydrous DMF a few crystals of KI was added. Shaked well the reaction mixture and then heated on water bath at 75–80°C for 12 hours. The solvent was removed by distillation under reduced pressure dial. Water (about 50 ml) was added to the residue in order to dissolve inorganic salts. Precipitate separated was filtered, washed well with water, and crystallized from ethanol 96% from ethanol 96% from with activated charcoal to obtain corresponding 5-methyltetrazolo[1,5-*a*]quinolines **5a**, **5b** or **5f**.

5a, R=H: Pale beige solid, yield 71.9%, mp 199–200°C. IR (KBr) ν (cm⁻¹): 1620, 1564, 1500, 1449, 1373. ¹H NMR (500.13 MHz, DMSO-*d*₆) δ (ppm): 8.84 (d, 1H, *J* = 7.5 Hz, H-9), 8.63 (d, 1H, *J* = 8.0 Hz, H-6), 7.99–7.98 (m, 1H, H-8), 7.96 (s, 1H, H-4), 7.85 (t, 1H, *J* = 7.25

Hz, H-7), 2.75 (s, 3H, 5-Me). ^{13}C NMR (125.75 MHz, DMSO- d_6) δ (ppm): 147.3 (C-3), 142.7 (C-1), 131.8 (C-5), 130.2 (C-8), 128.5 (C-7), 126.9 (C-6), 124.4 (C-10), 116.9 (C-9) và 111.5 (C-4), 19.5 (5-Me).

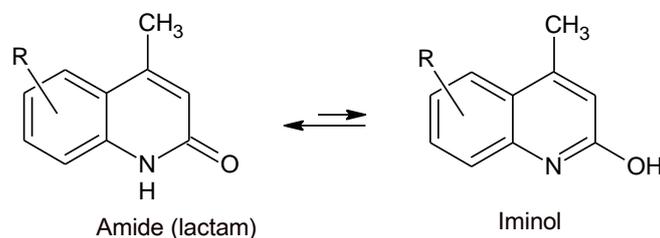
5b, R=7-Me: White crystal, yield 58.6%, mp 98–99°C. IR (KBr) ν (cm^{-1}): 1635, 1565, 1510, 1450, 1373. ^1H NMR (500.13 MHz, DMSO- d_6) δ (ppm): 7.80 (d, 1H, $J = 8.5$ Hz, H-9), 7.84 (s, 1H, H-4), 7.62 (dd, 1H, $J = 1.75, 8.5$ Hz, H-8), 7.38 (d, 1H, $J = 1.75$ Hz, H-6), 2.63 (d, 3H, $J = 1.0$ Hz, 5-Me), 2.51 (s, 3H, 7-Me). ^{13}C NMR (125.75 MHz, DMSO- d_6) δ (ppm): 149.1 (C-3), 148.5 (C-1), 145.9 (C-4), 137.1 (C-7), 133.0 (C-8), 128.5 (C-9), 127.0 (C-10), 123.8 (C-6), 122.5 (C-4), 18.4 (5-Me), 21.7 (7-Me),

5f, R=6-OMe: White solid, yield 90%, mp 150–151°C. IR (KBr) ν (cm^{-1}): 1630, 1574, 1503, 1460, 1377. ^1H NMR (500.13 MHz, DMSO- d_6) δ (ppm): 7.84 (d, 1H, $J = 9.0$ Hz, H-9), 7.44 (dd, 1H, $J = 9.0, 3.0$ Hz, H-8), 7.41 (d, 1H, $J = 0.5$ Hz, H-4), 7.33 (d, 1H, $J = 3.0$ Hz, H-6), 3.94 (s, 3H, 7-OMe), 2.65 (d, 3H, $J = 0.5$ Hz, 5-Me). ^{13}C NMR (125.75 MHz, DMSO- d_6) δ (ppm): 158.1 (C-7), 147.9 (C-3), 147.4 (C-1), 143.2 (C-5), 130.3 (C-9), 128.2 (C-10), 122.9 (C-8), 122.7 (C-4), 103.5 (C-6), 56.1 (7-Me), 18.7 (5-Me).

3. Results and Discussion

The transformation reaction of ethyl acetoacetat with (un)substituted anilines **1** into corresponding acetoacenilindes **2** considered completely when ethanol formed was no longer distilled. Then, the solvent was removed entirely, the residue consists mostly of acetoacetanilide used to direct ring-closure into 4-methylquinolin-2(1*H*)-ones **3** without isolation. We found that the use of concentrated 98% sulfuric acid was not suitable for this cyclizing reaction due no product was obtained or yields were very low. The concentration of sulfuric acid was >80% also receive the results are not satisfactory. Through a survey about influence of the concentration of sulfuric acid to obtained yields of 4-methylquinolin-2(1*H*)-one, we found that concentrations of sulfuric acid were 70–72% were most appropriate for the above conversion of acetoacetanilides to corresponding 4-methylquinolin-2(1*H*)-ones. The smaller concentrations of sulfuric acid did not promote the reaction (*Scheme 1*).

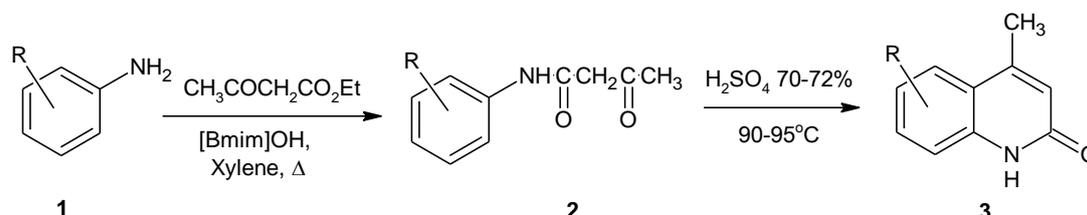
IR spectra of these quinolines **3** had some characteristic absorption bands, such as $3454\text{--}3341\text{ cm}^{-1}$ ($\nu_{\text{NH}_{\text{lactam}}}$), 1537 cm^{-1} ($\delta_{\text{NH}_{\text{lactam}}}$), 1657 cm^{-1} ($\nu_{\text{C=O}_{\text{lactam}}}$). In ^1H NMR spectra, chemical shift was in region of 11.60–11.40 ppm belonging to NH bond in lactam. Carbon atom in carbonyl had resonance signals at $\delta = 160\text{--}150$ ppm. We found that some of substituted 4-methylquinolin-2(1*H*)-ones (**3e** and **3h**) showed the existence of amide-iminol tautomerism below:



Amide tautomer was characterized by ^1H NMR signals of the NH(lactam) bond at $\delta = 8.07$ ppm, and C=O(lactam) at $\delta = 153.6$ ppm, meanwhile, iminol tautomer had chemical shift at $\delta = 12.17$ ppm (OH phenol type), and the signal of C-2 carbon atom moved about more upfield, $\delta = 148.7$ ppm.

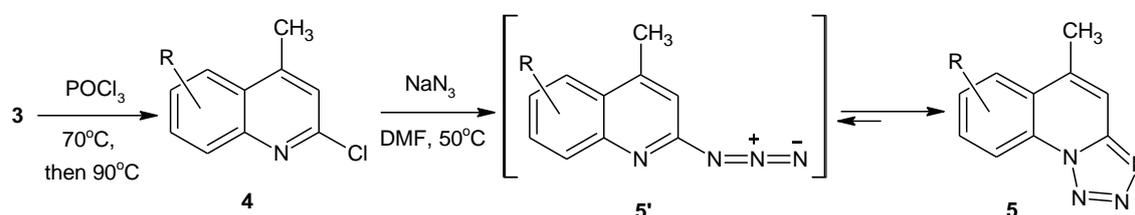
In order to convert 4-methyl-quinoline-2(1*H*)-ones **3** to the chloro derivatives **4a-d**, respectively, the former allowed to react with POCl_3 at temperatures of 70–90°C (*Scheme 2*).

Yields were 86–90%. IR spectra of 2-chloro-4-methylquinolines **4** had some characteristic absorption bands, such as $3057\text{--}3120\text{ cm}^{-1}$ ($\nu_{\text{C-H}}$ quinoline), 763 cm^{-1} ($\nu_{\text{C-Cl}}$), $1530\text{--}1660\text{ cm}^{-1}$ ($\nu_{\text{C=C}}$ aromatic). ^1H NMR spectra of 2-chloro-4-methylquinolines **4** had two regions of signals: aromatic ($\delta = 8.0\text{--}7.0\text{ ppm}$) and aliphatic ($\delta \approx 2.7\text{ ppm}$). ESI-MS of **4a**, for example, had two peaks which had mass number of m/z 178 and m/z 180, with relative intensities were 31% and 100%, related to two pseudo-maleoconic ions $[\text{M}+\text{H}]^+$ and $[\text{M}+\text{H}+2]^+$, respectively, this accord with the presence of one chlorine atom in that molecule.



Scheme 1. Synthesis of substituted 4-methylquinolin-2(1*H*)-ones, where, R=H (**a**), 6-CH₃ (**b**), 7-CH₃ (**c**), 8-CH₃ (**d**), 6,8-diCH₃ (**e**), 6-OCH₃ (**f**), 7-OCH₃ (**g**), 6-OC₂H₅ (**h**).

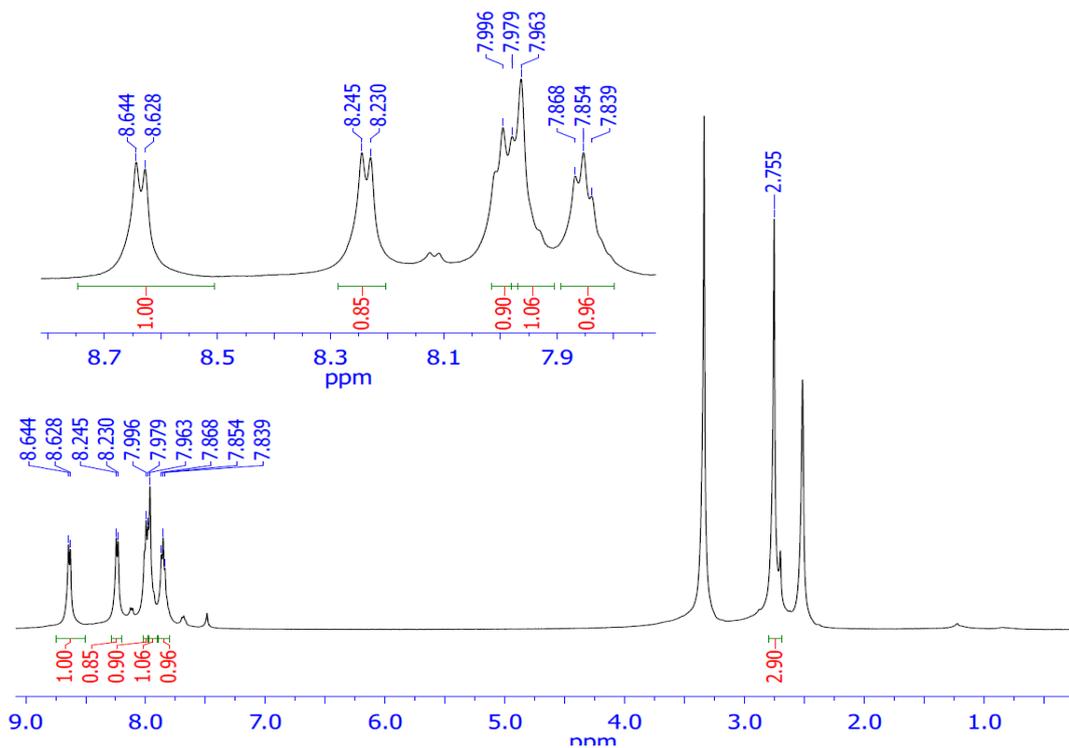
Next, substituted 2-chloro-4-methylquinolines **4** allow to react with sodium azide in DMF. Reaction proceeded at 70°C. In comparison with reaction of the 4-chloro-2-methylquinolines with sodium azide that give corresponding 4-azido-2-methylquinolines [6], the reaction 2-chloro-4-methylquinolines with sodium azide does not lead to the corresponding azido derivatives, but azido intermediates **5'** ring-closure itself into fused-ring system of tetrazolo [1,5-*a*]quinoline **5** (*Scheme 2*).



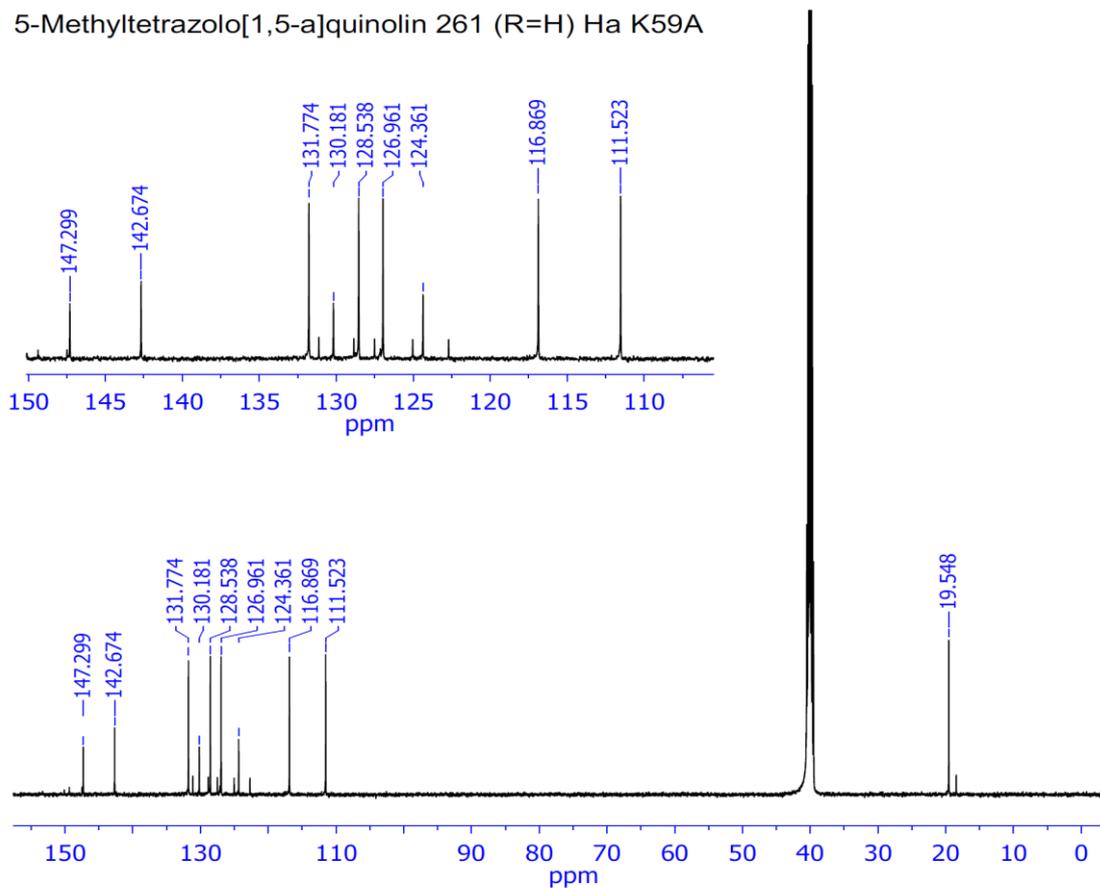
Scheme 2. Conversion of substituted 4-methylquinolin-2(1*H*)-ones to corresponding (un)substituted 5-methyltetrazolo[1,5-*a*]quinolines, where, R=H (**a**), 6-CH₃ (**b**), 7-CH₃ (**c**), 8-CH₃ (**d**), 6,8-diCH₃ (**e**), 6-OCH₃ (**f**).

The conversion of 2-chloro-4-methylquinolines to tetrazolo[1,5-*a*]quinolines through the 2-azido-4-methylquinolines, respectively, were performed in DMF as solvent. This solvent helps dissolved the compound 2-chloroquinolines as well as sodium azide to facilitate the reaction. After the reaction, the tetrazolo[1,5-*a*]quinolines are dark yellow solid, have high melting temperature, soluble in DMF, DMSO, slightly soluble in ethanol, methanol.

In IR spectra of all tetrazolo[1,5-*a*]quinolines **5a-f** had not absorption bands in the region of $2200\text{--}2100\text{ cm}^{-1}$ of azido group. This indicated that the 2-azido compounds did not exist, but instead of the fused heterocycle, namely tetrazolo[1,5-*a*]quinoline.



5-Methyltetrazolo[1,5-a]quinolin 261 (R=H) Ha K59A



The typical signal for all protons of the compound 5a-f appeared in ^1H NMR spectra.

Methyl group in the position 5 on the quinoline ring component had chemical shift in the upfield region at $\delta \approx -2.75$ ppm (as singlet). The signals were located in the downfield region at $\delta=8.7-7.4$ ppm belonging to 4 protons of tetrazolo[1,5-*a*]quinoline. Proton H-4 has a chemical shift at $\delta=7.96$ ppm in singlet in **5a**. Resonance signal of proton H-6 was downfield at $\delta=8.63$ ppm as doublet with the coupling constant of $J=8.0$ Hz (Fig. 1). Chemical shift at $\delta=8.84$ ppm belonged to proton H-9 as doublet with $J=7.5$ Hz. Multiplet signal in region at $\delta=7.99-7.98$ ppm belonged to the proton H-8; Meanwhile, proton H-7 had resonance at $\delta=7.85$ ppm as triplet with $J=7.25$ Hz. Amongst the protons in benzene component of quinoline ring, this proton had a resonance in the strongest field. Chemical shifts of all carbon atoms in quinoline ring located in range of $\delta = 148-110$ ppm (Fig. 2).

In brief, the Knorr cyclization of (un)substituted acetoacetanides have been performed by using ionic liquid [Bmim]OH as catalyst. Some substituted 4-methylquinolin-2(1*H*)-ones have been synthesized and converted to tetrazolo[1,5-*a*]quinoline via chloro derivatives. Their structure were confirmed by IR, NMR and MS methods.

References

- [1] Heeb S., Fletcher M.P., Chhabra S.R., Diggle S.P., Williams P., Cámara M. (2011), "Quinolones: from antibiotics to autoinducers", *FEMS Microbiology Reviews*, 35(2), 247-274.
- [2] Acar J.F., Goldstein F.W. (1997), "Trends in bacterial resistance to fluoroquinolones", *Clinical Infectious Diseases*, 24 (Suppl. 1), S67-S73.
- [3] Ismail M.M., Abass M. and Hassan M.M. (2000), "Chemistry of Substituted Quinolinones. Part VI.† Synthesis and Nucleophilic Reactions of 4-Chloro-8-methylquinolin-2(1*H*)-one and its Thione Analogue", 5, 1224-1239.
- [4] Welton T. (1999), "Room-Temperature Ionic Liquids. Solvents for Synthesis and Catalysis", *Chemical Reviews*, 99, 2071-2083.
- [5] Nguyen Dinh Thanh, Le The Hoai, Nguyen Thi Kim Giang and Nguyen Van Quoc (2016), "Ionic Liquids as Catalyst for Synthesis of Some Aromatic Peracetylated *N*-(β -D-Glucopyranosyl)Thiosemicarbazones", *Current Organic Synthesis*, 13(5), 767-775.
- [6] Le The Duan, Nguyen Dinh Thanh, Tran Thi Thanh Van, Luu Son Quy, Doan Thi Hien, Pham Thi Anh (2017), "Study on synthesis of some substituted 4-azido-2-methylquinolines from 4-hydroxy-2-methyl-4-(1*H*)-quinolin-4-ones", *Vietnam Journal of Chemistry*