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L.D. Bolibrukh, I.I. Hubytska, A.I. Karkhut, R.T. Konechna, S.V. Polovkovych, V.P. Novikov

THE STUDY OF THE INTERACTION OF 2-CHLORO- AND 2,3-DICHLORO-5(8)-RO-1,4-NAPHTOQUINONES WITH CH-ACIDS

Lviv Polytechnic National University, Lviv, Ukraine

The regioselectivity of the reaction of 2-chloro- and 2,3-dichloro-5-substituted naphthoquinones with CH-acids is studied. It is shown that the nature of the substituent in 5-RO-1,4-naphthoquinones plays the main role in the predominant formation of one of the possible regioisomers in the reactions of nucleophilic substitution. It is substantiated that the orientation of the nucleophilic attack by CH-acid on the C^3 atom of 5-RO-1,4-naphthoquinones is due to the fact that the 5-methoxy and 5-acetoxy groups have a passivating effect on the electron-accepting properties of the C^4=O group due to the positive conjugation effect. As a result, the electrophilic center appears in position 3. It is established that the interaction of 2- or 3-chloro-substituted 5-RO-1,4-naphthoquinones with CH-acids proceeds with the formation of 2- and 3-addition products with a preference for products of substitution of the chlorine atom in 3rd position. The structure of the regioisomers is confirmed by spectral data and by countersynthesis.

Keywords: naphthoquinone derivative, CH-acid, Michael addition, nucleophilic substitution, regioselectivity.

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Introduction

Naphthoquinones are the most common type of quinones in nature. They are a diverse family of derivatives that are naturally found in plants, lichens and various microorganisms. In recent decades, a number of new 1,4-naphthoquinones have been isolated from natural sources [1] and new 1,4-naphthoquinones with different structural features have been synthesized [2–5]. Cardioprotective, anti-ischemic, hepatoprotective, neuroprotective [6] and some other properties have been found for these compounds. Their anti-inflammatory [7], antimicrobial [8,9], antiprotozoal [10], antiviral [11], antithrombotic [12] and antitumor [13] activities have been studied in more detail. New, previously unknown intracellular molecular targets and mechanisms of action were discovered [14]. Some compounds of this class are already used as drugs, and some substances are at various stages of research. Considering the wide spectrum of biological activity of 1,4-naphthoquinone derivatives, the synthesis of new compounds based on it is an actual task.

It is known that in nucleophilic substitution reactions in a number of 1,4-naphthoquinones, the nature of the substituent plays a major role in the predominant formation of one of the possible regioisomers. The presence of an electron-donating substituent in the 5-position of naphthalene-1,4-dione directs the attack to the 3-position due to the creation of a partial positive charge, and the presence of an electron-withdrawing substituent directs the attack to the 2-position of naphthalene-1,4-dione, which was shown in study [15].

Therefore, the aim of our work was to investigate the effect of O-methoxy and acetoxy substituents in the 5th position of chlorinated 1,4-naphthoquinones on the regioselectivity of the reaction with CH acids – acetylacetone and acetylacetone.

Experimental

General methods

All the chemicals were purchased from Aldrich Chemical Company (USA) and used without further purification. Melting points were determined on a Bьchi capillary melting point apparatus and are uncorrected. The elemental analyses were performed

using the Perkin-Elmer 2400 CHN analyzer. ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer. The ^{1}H chemical shifts are reported from TMS. IR spectra were recorded on Specord M-80 IR spectrophotometer within the range of 4000−500 cm^{-1} in KBr tablets.

TLC was performed on 5 cmr10 cm aluminum plates coated with silica gel 60 F254 (Merck) in an appropriate solvent. Preparative chromatography was performed on «LS 5/40» silica gel, kieselgel-60 plates (Merck).

General procedure for the synthesis

1. 2-Chloro-3-(2,4-dioxopentan-3-yl)-5-methoxynaphthalene-1,4-dione (5)

A. A solution of 2-chloro-5-methoxy-1,4-naphthoquinone (1) (0.90 g, 0.004 mol), acetylacetone (4) (0.40 g, 0.004 mol) and triethylamine (0.41 g, 0.004 mol) in 50 ml of dry methanol was kept at 40^{0}C for 4 hours, after which air was passed through the reaction mixture for 2 hours. The solvent was partially removed under vacuum, the precipitate that fell out was filtered, washed with water, dried in a vacuum, and crystallized from toluene. Yield 0.64 g (49%), brownish crystals, m.p. 218−219^{0}C (toluene). ^{1}H NMR (DMSO-d6, 200 MHz): δ (ppm) 9.04 (s, 1H, OH), 7.84 (d, J=7.5 Hz, 1H, quinone), 7.76 (t, J=7.6 Hz, 1H, quinone), 7.68 (d, J=7.8 Hz, 1H, quinone), 3.72 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3), 2.16 (s, 3H, CH_3). IR (KBr): 1680, 1668, 1632, 1628 (C=O), 1610, 1604, 1592, (C=C), 1290 (C−O−C). Calculated ($C_{16}H_{13}ClO_5$), %: C 59.92; H 4.09; Cl 11.05. Found, %: C 59.78; H 3.99; Cl 10.97.

B) To a solution of 1.5 g (0.0058 mol) of 2,3-dichloro-5-methoxy-1,4-naphthoquinone (11) and 0.59 g (0.0058 mol) of triethylamine in 100 ml of dry methanol with intensive stirring at 20^{0}C a solution of 0.58 g (0.0058 mol) of acetylacetone (4) in 20 ml of methanol was added for 0.5 hour. The reaction mixture was kept for 4 hours, and the solvent was removed under vacuum. The resinous residue was dissolved in 50 ml of a mixture (benzene/ethyl acetate=4:1), the organic layer was washed three times with portions of 50 ml of water, dried with anhydrous magnesium sulfate, and filtered. The filtrate was purified by preparative chromatography on plates (eluent − benzene/ethyl acetate=4:1, R_f=0.82), a yellow-orange crystals were isolated with the yield 0.75 g (40%). Physicochemical constants of substances obtained by methods A and B are identical.

2. 3-Chloro-2-(2,4-dioxopentan-3-yl)-5-methoxynaphthalene-1,4-dione (6)

A. It was synthesized in the same way as compound (5), method A. From 1.8 g (0.008 mol) of 2-chloro-8-methoxy-1,4-naphthoquinone (2), 0.81 g (0.008 mol) acetylacetone (4) and 0.82 g (0.008 mol) of triethylamine 1.02 g (39%) of title compound was obtained, m.p. 232^{0}C, brownish crystals. ^{1}H NMR (DMSO-d6, 200 MHz): δ (ppm) 9.14 (s, 1H, OH), 7.95−7.75 (m, 2H, quinone), 7.63 (d, J=8.0 Hz, 1H, quinone), 3.77 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3), 2.13 (s, 3H, CH_3). IR (KBr): 1684, 1662, 1605, 1560 (C=O), 1610, 1600, 1590 (C=C), 1290 (C−O−C). Calculated ($C_{16}H_{13}ClO_5$), %: C 59.92; H 4.09; Cl 11.05. Found, %: C 59.88; H 4.01; Cl 9.96.

B. It was isolated by preparative chromatography from the reaction mixture obtained similarly to compound (5), method B (eluent − benzene/ethyl acetate=4:1, R_f=0.84). Yellow-orange crystals, yield 10%. Physicochemical constants of substances obtained by methods A and B are identical.

3. 6-Chloro-7-(2,4-dioxopentan-3-yl)-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate (7)

A. It was obtained similarly to compound (5) under the conditions of the method B. From 2.00 g (0.008 mol) of 5-acetoxy-2,3-dichloro-1,4-naphthoquinone (12), 0.81 g (0.008 mol) of triethylamine and 0.80 g (0.008 mol) of acetylacetone (4), (eluent − benzene/ethyl acetate=4:1, R_f=0.76). The yield was 48%, m.p. 183−184^{0}C (toluene). ^{1}H NMR (DMSO-d6, 200 MHz): δ (ppm) 9.10 (s, 1H, OH), 7.48−7.31 (m, 3H, quinone), 2.39 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.12 (s, 3H, CH_3). IR (KBr): 1684, 1668, 1632, 1628 (C=O), 1610, 1600, 1590 (C=C), 1286 (C−O−C). Calculated ($C_{17}H_{13}ClO_6$), %: C 58.55; H 3.76; Cl 10.17. Found, %: C 58.46; H 3.67; Cl 10.08.

B) A solution of 2.00 g (0.008 mol) of 5-acetoxy-2-chloro-1,4-naphthoquinone (3), 0.81 g (0.008 mol) of triethylamine, and 0.80 g (0.008 mol) of acetylacetone (4) in 150 ml of methanol was kept at 40^{0}C for 2 hours, after which air was bubbled through the reaction mass for 2 hours. The solvent was partially removed under vacuum. The formed precipitate was filtered, washed with water, dried in a vacuum, and crystallized from toluene. Yield 2.09 g (75%). Physicochemical constants of substances synthesized by methods A and B are identical.

4. Ethyl (3-chloro-8-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)(cyano)acetate (9)

A. To a solution of 1.00 g (0.0039 mol) of 2,3-dichloro-5-methoxy-1,4-naphthoquinone (11) in 100 ml of dry methanol, 0.38 g (0.41 ml, 0.0042 mol) of piperidine was added, and then, with stirring, 0.44 g (0.0039 mol) of ethyl cyanoacetate (8) was added.

The reaction mixture was kept at 40°C for 2 hours. The solvent was partially distilled off in a vacuum. After cooling, the reaction mass was filtered, the precipitate was dried in a vacuum, and crystallized from benzene. Yield 0.86 g (66%), m.p. 240–241°C. ^{1}H NMR (DMSO-d6, 200 MHz): δ (ppm) 7.79–7.68 (m, 2H, quinone), 7.55 (t, J=7.9 Hz, 1H, quinone), 5.21 (s, H, CH), 4.25 (q, J=7.1 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 1.38 (t, J=7.9 Hz, 3H, CH_3). IR (KBr): 2236 (C≡N), 1686, 1660 (C=O), 1610, 1600, 1560 (C=C), 1286 (C–O–C). Calculated ($C_{16}H_{12}ClNO_5$), %: C 57.58; H 3.62; Cl 10.62; N 4.20. Found, %: C 57.65; H 3.70; Cl 10.57; N 4.29.

B) A solution of 0.20 g (0.0009 mol) of 2-chloro-5-methoxy-1,4-naphthoquinone (1), ethyl cyanoacetate (8) (0.10 g, 0.0009 mol) and piperidine (0.08 g, 0.0009 mol) was stirred at 40°C in 100 ml of dry methanol for 2 hours. After stirring, the reaction mixture was bubbled with air at 20°C for 5 hours, the solvent was partially removed under vacuum. The precipitate that fell out was filtered, dried in a vacuum, and crystallized from benzene. Yield 0.17 g (57%). Physicochemical constants of substances obtained by methods A and B are identical.

5) Ethyl [8-(acetyloxy)-3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl](cyano)acetate (10)

A) 0.68 g (0.008 mol) of piperidine was added to a solution of 2.00 g (0.007 mol) of 5-acetoxy-2,3-dichloro-1,4-naphthoquinone (12) in 50 ml of dry methanol with vigorous stirring, and then 0.79 g (0.007 mol) of ethyl cyanoacetate (8) was added. The reaction mixture was kept at 40°C for 20 hours. The solvent was partially distilled off in a vacuum; the obtained precipitate was dried in a vacuum, and crystallized from toluene. Yield 1.72 g (68%), m.p. 214°C. ^{1}H NMR (DMSO-d6, 200 MHz): δ (ppm) 7.89–7.74 (m, 2H, quinone), 7.64 (d, J=7.9 Hz, 1H, quinone), 5.19 (s, H, CH), 4.24 (q, J=7.1 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3), 1.34 (t, J=7.1 Hz, 3H, CH_3). IR (KBr): 2232 (C≡N), 1740, 1680, 1664 (C=O), 1610, 1600, 1560 (C=C), 1282 (C–O–C). Calculated ($C_{28}H_{19}ClNO_9$), %: C 56.45; H 3.34; Cl 9.80; N 3.87; Found, %: C 56.32; H 3.37; Cl 9.91; N 3.79.

B. A solution of 0.20 g (0.0009 mol) of 5-acetoxy-2-chloro-1,4-naphthoquinone (3), ethyl cyanoacetate (8) (0.10 g, 0.0009 mol) and piperidine (0.08 g, 0.0009 mol) was stirred at 40°C in 100 ml of dry methanol for 2 hours. After stirring, the reaction mixture was bubbled with air at 20°C for 5 hours, the solvent was partially removed under vacuum. The precipitate that fell out was filtered, dried in a vacuum, and crystallized from benzene. Yield 0.22 g (68%). Physicochemical constants of substances obtained by methods A and B are identical.

6. 7-Chloro-6-(2,4-dioxopentan-3-yl)-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate (13)

It was isolated by preparative chromatography from the reaction mixture obtained similarly to the preparation of compound (7), method A (eluent benzene/ethyl acetate=4:1, R_f=0.73). Yield 11%, m.p. 197°C (toluene). ^{1}H NMR (DMSO-d6, 200 MHz): δ (ppm) 9.11 (s, 1H, OH), 7.95–7.75 (m, 3H, quinone), 2.38 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.14 (s, 3H, CH_3). IR (KBr): 1688, 1662, 1608, 1560 (C=O), 1610, 1600, 1590 (C=C), 1292 (C–O–C). Calculated ($C_{17}H_{13}ClO_6$), %: C 58.55; H 3.76; Cl 10.17. Found, %: C 58.47; H 3.68; Cl 10.09.

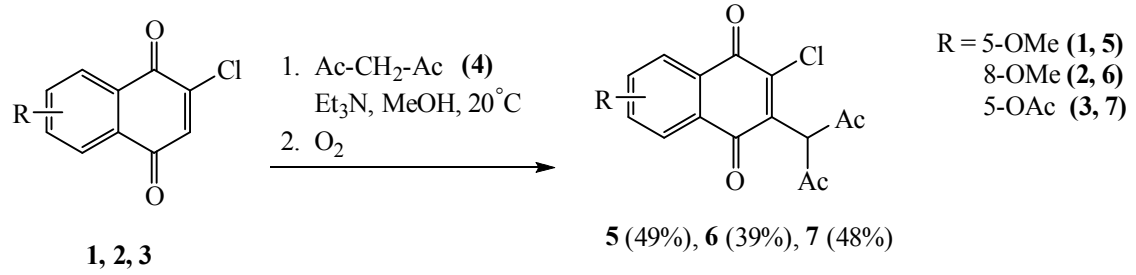
7. Ethyl (3-chloro-5-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)(cyano)acetate (14)

It was obtained similarly to compound (9) under the conditions of the method A. From 1.00 g (0.0039 mol) of 2,3-dichloro-5-methoxy-1,4-naphthoquinone (11), 0.4 g (0.36 ml, 0.0042 mol) of piperidine, 0.44 g (0.0039 mol) of ethyl cyanoacetate (8). The product was isolated by preparative chromatography (eluent benzene/ethyl acetate=4:1, R_f=0.80). Yield 0.10 g (8%), m.p. 188–189°C (toluene). ^{1}H NMR (DMSO-d6, 200 MHz): δ (ppm) 7.90–7.71 (m, 2H, quinone), 7.59 (d, J=8.0 Hz, 1H, quinone), 5.21 (s, H, CH), 4.24 (q, J=7.1 Hz, 2H, CH_2), 3.78 (s, 3H, OCH_3), 1.37 (t, J=7.1 Hz, 3H, CH_3). IR (KBr): 2232 (C≡N), 1740, 1680, 1664 (C=O), 1610, 1600, 1560 (C=C), 1282 (C–O–C). Calculated ($C_{16}H_{12}ClNO_5$), %: C 57.58; H 3.62; Cl 10.62; N 4.20; Found, %: C 57.65; H 3.55; Cl 10.71; N 4.26.

Results and discussion

We have established that in the case of 5- or 8-methoxy- and 5-acetoxy-monohalogen substituted naphthoquinones (1,2,3) the main center attacked by the nucleophilic reagent is the unsubstituted carbon atom in position 3 of the quinoid nucleus by Michael reaction.

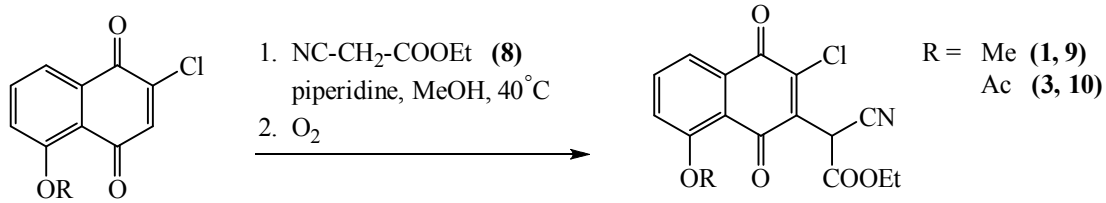
The interaction of acetylacetone (4) with 2-chloro- (1), 3-chloro-5-methoxy-1,4-naphthoquinone (2) and 2-chloro-5-acetoxy-1,4-naphthoquinone (3) by the Michael reaction leads to obtaining 3-(2-hydroxy-4-oxopenten-2-yl-3)-2-chloro-5-methoxy-1,4-naphthoquinone (5), 2-(2-hydroxy-4-oxopenten-2-yl-3)-3-chloro-5-methoxy-1,4-naphthoquinone (6) and 3-(2-hydroxy-4-oxopenten-2-yl-3)-2-chloro-5-acetoxy-1,4-naphthoquinone (7) (Scheme 1). It was possible to increase the yield of products (5,6,7) by passing of the air through the reaction mixture in order to oxidize 1,4-diole, which is formed as an intermediate product of Michael addition, to quinone.



1, 2, 3

5 (49%), **6** (39%), **7** (48%)

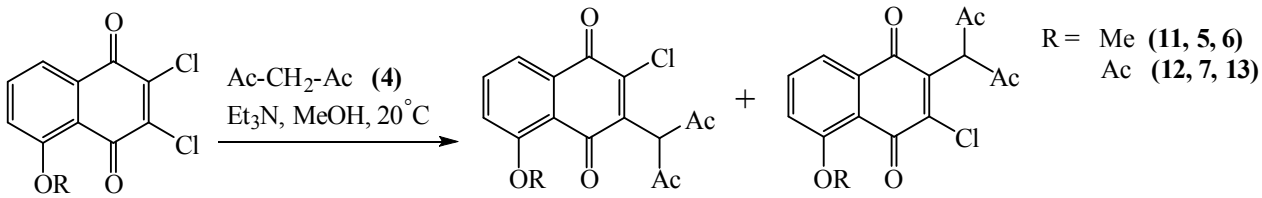
Scheme 1



1, 3

9 (57%), **10** (68%)

Scheme 2



11, 12

5 (40%), **7** (75%)

6 (10%), **13** (11%)

Scheme 3

In the case of studying the interaction of monohalogen-substituted 1,4-naphthalenediones (1,2,3) with ethyl cyanoacetate in methyl alcohol in the presence of piperidine, it was possible to obtain products only for reagents (1,3) (Scheme 2).

The structures of naphthoquinones (5,6,7) were confirmed by the results of elemental analysis and spectral data. In the IR spectra of compounds (5,6), characteristic absorption bands of the carbonyl groups of the quinoid ring are observed in the region of 1668–1680 cm^{-1} and for the acetylacetone fragment at 1632–1628 cm^{-1}.

In the ^1H NMR spectrum of 3-(2-hydroxy-4-oxopenten-2-yl-3)-2-chloro-5-methoxy-1,4-naphthoquinone (5) in DMSO-d6 solution, characteristic shifts of protons are observed: singlets of two methyl groups at 2.16 ppm and 2.30 ppm, singlet of the methoxyl group at 3.72 ppm, a characteristic shifts of protons of the aromatic ring at 7.84 ppm (d, J=7.5 Hz), 7.76 ppm (t, J=7.6 Hz), 7.68 ppm (d, J=7.8 Hz), and a broadened singlet of enol hydroxyl at 9.04 ppm. The presence of a signal at 9.04 ppm indicates the possibility of the existence of compound (5) in the solution in the enol form.

As we predicted, 2,3-dichlorosubstituted naphthoquinones (11,12) very easily react by nucleophilic substitution of a chlorine atom on the carbanionic residue of CH-acids (4,8). The presence of a methoxy group, as well as an acetoxy group in the 5th position of the investigated naphthalene-1,4-dione derivatives increases the reactivity of the C^3 position of quinoid nucleus in reaction with nucleophilic reagents. This is due to the fact that in these compounds the RO group have the positive conjugation effect, which causes passivating effect on the electron-accepting properties of the C^4=O group, and therefore the electrophilic center appears at the C^3 atom. This is confirmed by the predominant yield of the 3-substituted product in the reactions of 5-methoxy- (11) and 5-acetoxy-2,3-dichloro-1,4-naphthoquinone (12) with carbanions of CH-acids (4,8) (Scheme 3).

During the interaction of 2,3-dichloro-5-methoxy-1,4-naphthoquinone (11) with

acetylacetone (4) by nucleophilic substitution reaction, the main product of the reaction, as expected, is 3-(2-hydroxy-4-oxopenten- 2-yl-3)-5-methoxy-2-chloro-1,4-naphthoquinone (5) (R_f=0.82), it is a product of substitution of the chlorine atom in the third position. It is identical to the substance (5), which was obtained as a final result of the interaction of 2-chloro-5-methoxy-1,4-naphthoquinone (1) with acetylacetone (4) followed by oxidation (Scheme 1). 2-Substituted product (6) (R_f=0.84) is formed in much less amount. The ratio of the 3-substituted product (5) to the regioisomer (6) is approximately 4:1. The identification of (6) was carried out by comparing of the ^{1}H NMR, IR spectra, TLC and mixing sample with 2-(2-hydroxy-4-oxopenten-2-yl-3-)-5-methoxy-3-chloro-1,4-naphthoquinone (6), obtained in an alternative way: by adding acetylacetone (4) to 3-chloro-5-methoxy-1,4-naphthoquinone (2). A mixture of products (6) obtained in different ways does not cause depression of the melting point. The interaction of 2,3-dichloro-5-acetoxy-1,4-naphthoquinone (12) with acetylacetone (Scheme 3) proceeds in the same way as with 2,3-dichloro-5-methoxy-1,4-naphthoquinone (11).

It should be noted that the IR spectrum of the 2-chloro-3-substituted product (5) is similar in nature to the absorption bands, but differs from the 3-chloro-2-substituted (6) in the «fingerprint» region, that is, below 1400 cm^{-1}, allows ascertaining the formation of the isomeric product (6). The difference in melting temperatures of compounds (5) and (6), very close R_f values (0.82 and 0.84, respectively), as well as equivalent elemental analysis data fully confirm the isomerism of substances (5) and (6).

The same features are observed in other cases: when 2,3-dichloro-5-methoxy-1,4-naphthoquinone (11) and 2,3-dichloro-5-acetoxy-1,4-naphthoquinone (12) interact with ethyl cyanoacetate (8). Thus, in the case of interaction of (11) with ethyl cyanoacetate (8) in methyl alcohol in the presence of piperidine, a multicomponent mixture of reaction products is formed, but the main ones are 3-(1-ethoxycarbonyl-1-cyanomethyl)-2-chloro-5-methoxy-1,4-naphthoquinone (9) (65%) and its isomer 2-(1-ethoxycarbonyl-1-cyanomethyl)-3-chloro-5-methoxy-1,4-naphthoquinone (14) (8%) (Scheme 4).

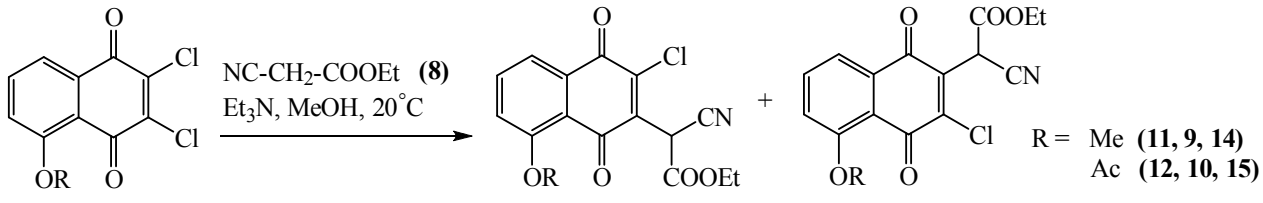
The identification of the 3-substituted product (10) was carried out by comparing the ^{1}H NMR, IR spectra and melting point of the mixing sample with 3-(1-ethoxycarbonyl-1-cyanomethyl)-2-chloro-5-methoxy-1,4-naphthoquinone (9), obtained by an alternative method: by adding ethyl cyanoacetate (8) to 2-chloro-5-methoxy-1,4-naphthoquinone (1) (Scheme 2).

The IR spectra of the product (9) synthesized by different routes are identical. There are characteristic absorption bands at 2236 cm^{-1} for the CvN group, intense bands of valence vibrations of carbonyl groups at 1736 cm^{-1}, 1686 cm^{-1} and 1660 cm^{-1} of ester and quinoid groups, respectively at 1610 cm^{-1}, 1600 cm^{-1}, 1560 cm^{-1} absorption of double conjugated bonds, at 1240 cm^{-1} C–O–C bond oscillation.

In the ^{1}H NMR spectrum of product (9) in $CDCl_3$, a triplet of methyl group protons at 1.38 ppm (J=7.9 Hz), singlet protons of the methoxyl group at 3.75 ppm, a quartet of methylene protons at 4.25 ppm (J=7.1), the methine proton singlet at 5.21 ppm, a multiplet of two aromatic protons at 7.79–7.68 ppm and triplet of one quinone proton at 7.55 ppm (J=7.9 Hz) are observed.

Conclusions

It was shown that substituted 2-chloro-1,4-naphthoquinones interact with CH-acids by the Michael reaction at the free third position. Further oxidation by air of intermediately formed 1,4-dioles leads to the restoration of the quinoid system. 5-Substituted-2,3-dichloro-1,4-naphthoquinones interact with CH-acids by a nucleophilic substitution reaction with the formation of a mixture of regioisomers with the predominant formation of the 3rd position reaction product. Obtained regioisomers were isolated by preparative chromatography and identified by spectral data and countersynthesis.



11, 12 **9** (66%), **10** (68%) **14** (8%), **15** (-)

Scheme 4

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ВИВЧЕННЯ ВЗАЄМОДІЇ 2-ХЛОР- ТА 2,3-ДИХЛОР-5(8)-RO-1,4-НАФТОХІНОНІВ З СН-КИСЛОТАМИ

Л.Д. Болібрух, І.І. Губицька, А.І. Кархут, Р.Т. Конечна, С.В. Половкович, В.П. Новіков

Досліджено регіоселективність реакції 2-хлор- та 2,3-дихлор-5-заміщених нафтохінонів з СН-кислотами. Показано, що природа замісника в 5-RO-1,4-нафтохінонах має важливе значення у переважному утворенні одного з можливих регіоізомерів у реакціях нуклеофільного заміщення. Обгрунтовано, що напрямок нуклеофільної атаки СН-кислоти на атом C^3 5-RO-1,4-нафтохінонів зумовлена тим, що 5-метокси та 5-ацетокси групи пасивують електроноакцепторні властивості групи C^4=O за рахунок позитивного ефекту кон'югації. У результаті електрофільний центр виникає в положенні 3. Встановлено, що взаємодія 2- або 3-хлорзаміщених 5-RO-1,4-нафтохінонів з СН-кислотами протікає з утворенням продуктів 2 та 3-приєднання з перевагою продуктів заміщення атома хлору в 3-му положенні. Будова регіоізомерів підтверджена спектральними даними та зустрічним синтезом.

Ключові слова: похідні нафтохінону, СН-кислота, приєднання Міхаеля, нуклеофільне заміщення, регіоселективність.

THE STUDY OF THE INTERACTION OF 2-CHLORO- AND 2,3-DICHLORO-5(8)-RO-1,4-NAPHTOQUINONES WITH CH-ACIDS

L.D. Bolibrukh, I.I. Hubytska, A.I. Karkhut, R.T. Konechna, S.V. Polovkovych *, V.P. Novikov

Lviv Polytechnic National University, Lviv, Ukraine

*** e-mail: spolovkovych@ukr.net**

The regioselectivity of the reaction of 2-chloro- and 2,3-dichloro-5-substituted naphthoquinones with CH-acids is studied. It is shown that the nature of the substituent in 5-RO-1,4-naphthoquinones plays the main role in the predominant formation of one of the possible regioisomers in the reactions of nucleophilic substitution. It is substantiated that the orientation of the nucleophilic attack by CH-acid on the C^3 atom of 5-RO-1,4-naphthoquinones is due to the fact that the 5-methoxy and 5-acetoxy groups have a passivating effect on the electron-accepting properties of the C^4=O group due to the positive conjugation effect. As a result, the electrophilic center appears in position 3. It is established that the interaction of 2- or 3-chloro-substituted 5-RO-1,4-naphthoquinones with CH-acids proceeds with the formation of 2- and 3-addition products with a preference for products of substitution of the chlorine atom in 3rd position. The structure of the regioisomers is confirmed by spectral data and by countersynthesis.

Keywords: naphthoquinone derivative; CH-acid; Michael addition; nucleophilic substitution; regioselectivity.

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