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MANGANESE(III) ACETATE MEDIATED SYNTHESIS OF NEW ANGULAR AND LINEAR DIHYDROFUROQUINOLINONES

MEHTAP ÖZGÜR, MEHMET YILMAZ, AND A.TARIK PEKEL

Abstract. Angular (**3**) and linear (**4**) dihydrofuroquinolinone derivatives were prepared in 'one pot' reaction of 4-hydroxy-1-methyl-quinoline-2-one (**1**) with (E)-2-(1-phenylprop-1-en-2-yl)thiophene (**2**) in the presence of manganese(III) acetate. The structures of the compounds (**3** and **4**) were determined by MS, FTIR, ID and 2D NMR techniques. A possible reaction mechanism was also described.

1. Introduction

Quinolines are one of the most abundant molecules, naturally occurring compounds and commonly used as versatile intermediates in natural products synthesis [1,2]. Dihydrofuroquinolines are other important compounds that are widely distributed in nature (Fig. 1) and several methods for the synthesis of these compounds are described in the literature [3,4]. A commonly used to obtain dihydrofuroquinolines involves cyclization reactions of carbonyl compounds with alkenes or alkynes in the presence of metal salts [5-7]. Manganese(III) acetate was the most preferred oxidant [8-10] for radical cyclization reactions and naturally occurring *araliopsine* [11] is synthesized easily by this oxidant.

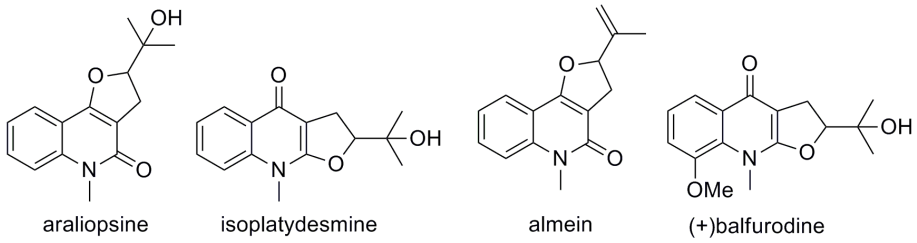

Figure 1. Naturally occurring dihydrofuroquinolinone compounds.

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Previously, we have reported $Mn(OAc)_3$ mediated synthesis of 4,5-dihydrofuran-3-carbonitriles [12], 3-trifluoroacetyl-4,5-dihydrofurans [13] and dihydrofuran [14] derivatives. Moreover, we have described the synthesis of dihydrofurocoumarin and dihydrofuronaphthoquinone derivatives in very good yields [15]. Also, we revealed the superior antibacterial and antifungal activity of 3-cyano-4,5-dihydrofuran derivatives compared with other antibacterial drugs [16].

Herein, we report the oxidative cyclization of 4-hydroxy-1-methyl-quinoline-2-one (1) with steric hindered alkene (E)-2-(1-phenylprop-1-en-2-yl)thiophene (2) by using electrochemically synthesized $Mn(OAc)_3$ which afforded 2,5-dimethyl-3-phenyl-2-(thiophen-2-yl)-2,3-dihydrofuro[3,2-c]quinolin-4(5H)-one (3, 39%) as an angular product and 2,9-dimethyl-3-phenyl-2-(thiophen-2-yl)-2,3-dihydrofuro[2,3-b]quinolin-4(9H)-one as a linear product (4, 28%) (Fig. 2).

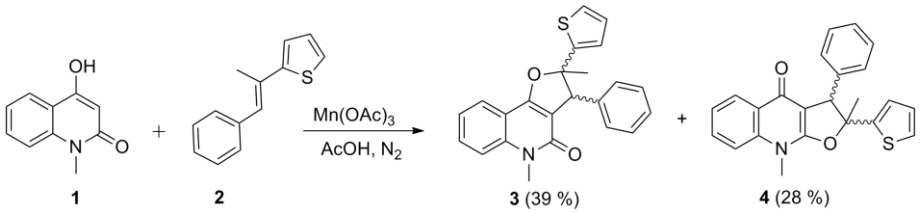

FIGURE 2. Reaction of 1 with 2.

2. MATERIALS AND METHODS

Physical measurements

Melting points were determined on a Gallencamp capillary melting point. IR spectra (KBr disc, $CHCl_3$) were obtained with a Matson 1000 FT-IR in the 400-4000 cm^{-1} range with 4 cm^{-1} resolution. ^1H NMR (400 MHz), and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance DPX-400 MHz and Varian Mercury-400 High performance Digital FT-NMR spectrophotometers. The mass spectra were measured on a Micromass UK LC/MS (APCI, 100-150 eV), and a Shimadzu GC-17A/GC-MS-QP5000 (EIMS, 70 eV) spectrophotometers. Elemental analyses were performed on a Leco 932 CHNS-O instrument. Thin layer chromatography (TLC) was performed on Merck aluminium-packed silica gel plates. Purification of products was performed by column chromatography on silica gel (Merck silica gel 60, 40-60 μm) or preparative TLC on silica gel of Merck (PF254-366 nm).

Materials used for syntheses

4-Hydroxy-1-methyl-quinoline-2-one (**1**) was purchased from Merck and was used without further purification. Manganese(III) acetate dihydrate was used as a radical oxidant was obtained from the bipolar packed-bed reactor by electrochemical method in literature [17].

2.3. Syntheses

*2.3.1. Syntheses of the new compounds (**3** and **4**)*

Manganese(III) acetate dihydrate (3 mmol) in 20 mL glacial acetic acid was heated under a nitrogen atmosphere at 80 °C until it dissolved. After $Mn(OAc)_3$ dissolved completely, a solution of **1** (2 mmol) and alkene **2** (1 mmol) in 5 mL acetic acid was added to this mixture. Reaction was monitored by TLC. When the reaction was complete, H_2O was added to the mixture and extracted with $CHCl_3$ (3x20 mL). The combined organic extracts were neutralized with saturated $NaHCO_3$ solution, and dried over anhydrous Na_2SO_4 and evaporated. The products were purified by column chromatography on silica gel or preparative TLC (20x20 cm plates, 2 mm thickness) using *n*-hexane/EtOAc (1/1) as an eluent.

*2.3.2 2,5-Dimethyl-3-phenyl-2-(2-thenyl)-3,5-dihydrofuro[3,2-c] quinoline-4H-one (**3**)*

Light yellow solid; mp: 160-161 °C; IR ($\nu_{max,}$ KBr): 3030 (Ar-H), 2927 (R-H), 1656 (C=O), 1637 (C=C), 1595, 1091, 750, 700; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.93 (1H, *dd*, *J*=8.0, 1.6 Hz, Ar***H***), 7.63 (1H, *td*, *J*=8.0, 1.6 Hz, Ar***H***), 7.41 (1H, *d*, *J*=8.4 Hz, Ar***H***), 7.34-7.27 (4H, m, Ar***H***), 7.21 (1H, *dd*, *J*=5.2, 1.2 Hz, Ar***H***), 7.15 (2H, *d*, *J*=6.4 Hz, Ar***H***), 7.11 (1H, *dd*, *J*=3.2, 0.8 Hz, Ar***H***), 6.96 (1H, *dd*, *J*=5.2, 4.0 Hz, Ar***H***), 4.93 (1H, *s*, ***H***3), 3.66 (3H, *s*, N-C***H***$_3$), 1.47 (3H, *s*, C***H***$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 26.32 (***C***H$_3$), 29.32 (***C***H$_3$), 59.14 (***C***3), 94.16 (*C*2), 110.85, 112.69, 114.86, 121.95, 123.13, 123.73, 124.76, 127.04, 127.83, 128.83 (***C***H*2), 128.94 (***C***H*2), 131.61, 137.68, 141.33, 151.17, 160.88 (***C***4), 162.03 (***C***9b); LC/MS, (ESI, m/z) : 374.44 (*M*H$^+$, 100); Anal. Calcd. for ($C_{23}H_{19}NO_2S$): C 73.97, H 5.13, N 3.75, S 8.59. Found: C 73.90, H 5.60, N 3.92, S 8.32.

*2.3.4 2,9-Dimethyl-3-phenyl-2-(2-thenyl)-3,9-dihydrofuro[2,3-b]quinoline-4(2H)-one (**4**)*

Light yellow solid; mp: 154-155 °C; IR ($\nu_{max,}$ KBr): 3030 (Ar-H), 2927 (R-H), 1616 (C=O), 1585 (C=C), 1537, 1512, 1211, 1060 (C-O-C), 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.42 (1H, *dd*, *J*=8.0; 1.6 Hz, Ar***H***), 7.63 (1H, *td*, *J*=7.8, 1.6 Hz, Ar***H***), 7.45 (1H, *d*, *J*=8.4 Hz, Ar***H***), 7.35 (1H, *td*, *J*=7.4, 1.2 Hz, Ar***H***), 7.32-7.25 (4H, *m*, Ar***H***), 7.18 (2H, *dd*, *J*=7.2, 2.0 Hz, Ar***H***), 7.15 (1H, dd, *J*=3.6, 1.2 Hz, Ar***H***), 6.99 (1H, *dd*, *J*=5.2, 3.6 Hz, Ar***H***), 5.09 (1H, s, ***H3***), 3.78 (3H, *s*, N-C**H**$_3$), 1.45 (3H, *s*, C***H***$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 26.17 (***C***H$_3$), 31.63 (***C***H$_3$), 57.56 (***C***3), 94.21 (***C***2), 101.48, 114.58, 123.54, 123.90, 125.31, 127.04, 127.16, 127.21, 127.69, 128.68 (***C***H*2), 128.94 (***C***H*2), 131.52, 137.62, 139.29, 149.76, 160.72 (***C***9a), 173.85 (***C***4); LC/MS, (ESI, m/z): 374.76 (*M*H$^+$, 100); Anal. Calcd. for ($C_{23}H_{19}NO_2S$): C 73.97, H 5.13, N 3.75, S 8.59. Found: C 73.87, H 5.35, N 3.57, S 8.45.

3. RESULTS AND DISCUSSION

(E)-2-(1-Phenylprop-1-en-2-yl)thiophene (**2**) were synthesized through Wittig method with benzyltriphenylphosphonium bromide and acetylthiophene [18]. During the radical cyclizations, effect of temperature and the molar ratio of product yield were investigated, and thus, the best results were obtained in glacial acetic acid at 80 °C in 20 minutes under nitrogen atmosphere using 2:1:3 molar ratio (1: 2: $Mn(OAc)_3$, respectively). After the work-up procedure, dihydrofuroquinolinones (**3** and **4**) were purified by column chromatography or preparative TLC and characterized by IR, ^{1}H NMR, ^{13}C NMR, 2D NMR, MS and microanalyses.

Two different dihydrofuroquinolinones (**3** and **4**) were synthesized from the reaction of 4-hydroxy-1-methyl-2*H*-quinoline-2-one (**1**) with (E)-2-(1-phenylprop-1-en-2-yl)thiophene (**2**). When NMR spectra of the compounds were examined, it was determined that **3** was an angular isomer, and **4** was a linear isomer. In the ^{1}H NMR spectrum of **4**, 9-H proton resonated as a *dd* at 7.93 ppm,while 5-H proton in **4** resonated as a *dd* at 8.42 ppm. Besides, in the ^{13}C NMR spectra of the compounds, settings of carbonyl group were determined at 160.88 and 173.85 ppm for **3** and **4**, respectively (Figs. 3 and 4). In the HSQC spectra of the compounds, it was found that thiophene and methyl groups were bound to ***C***2 carbon in both structures (Fig. 5).

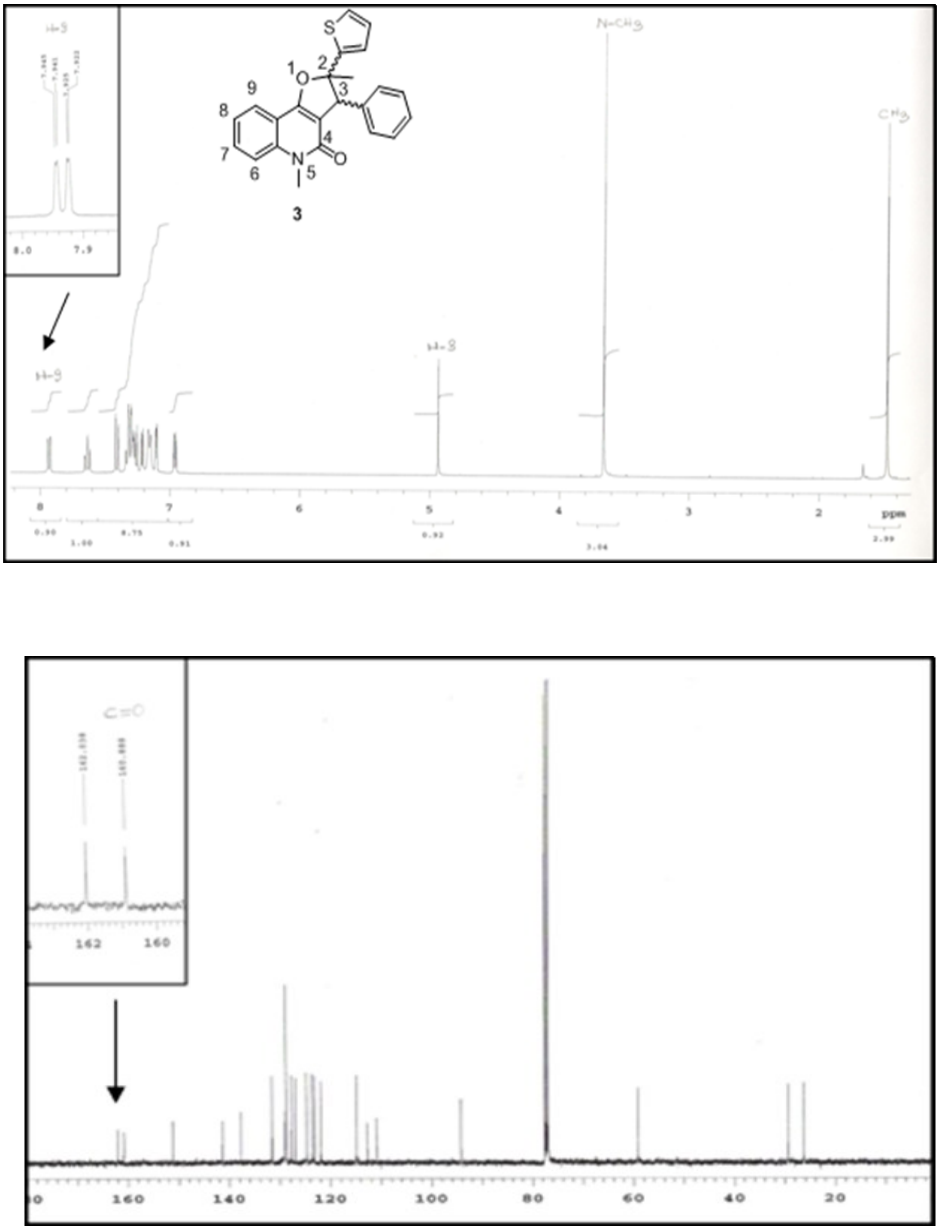

FIGURE 3. ^{1}H and ^{13}C NMR spectra of **3**.

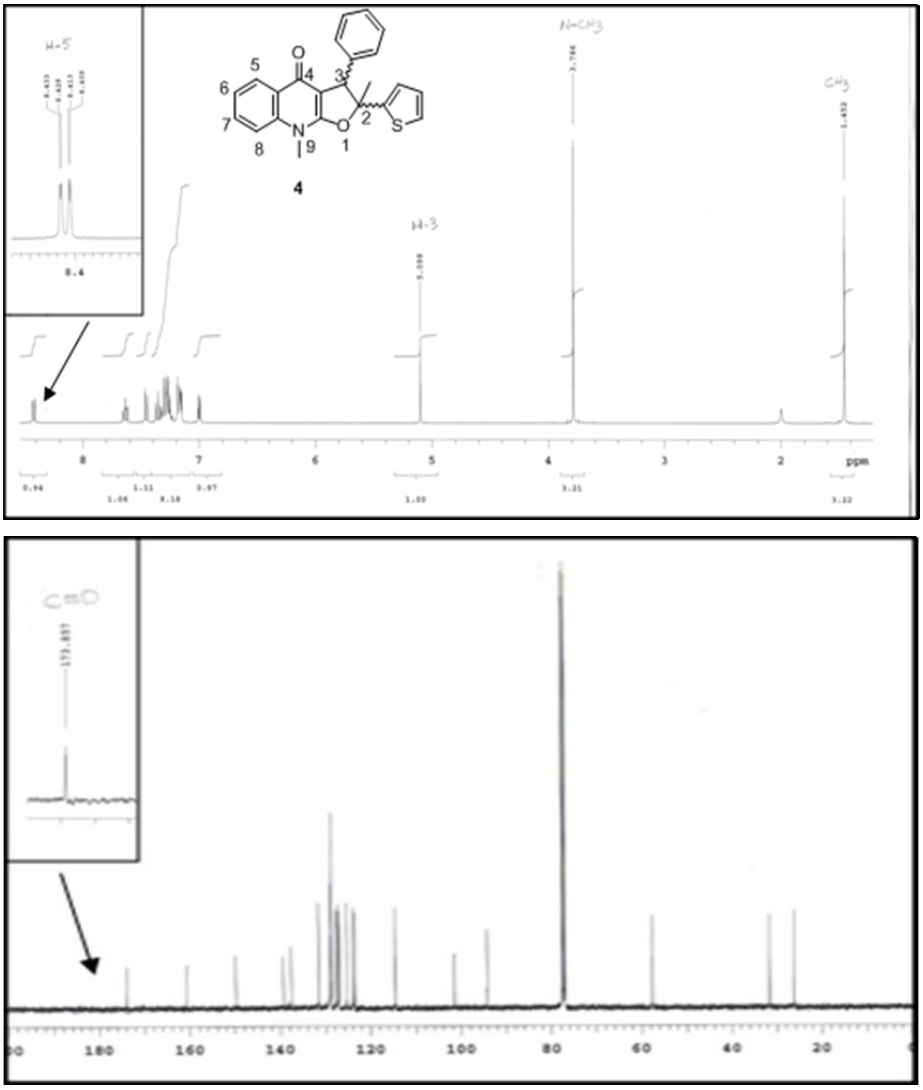

FIGURE 4. ^{1}H and ^{13}C NMR spectra of **4**.

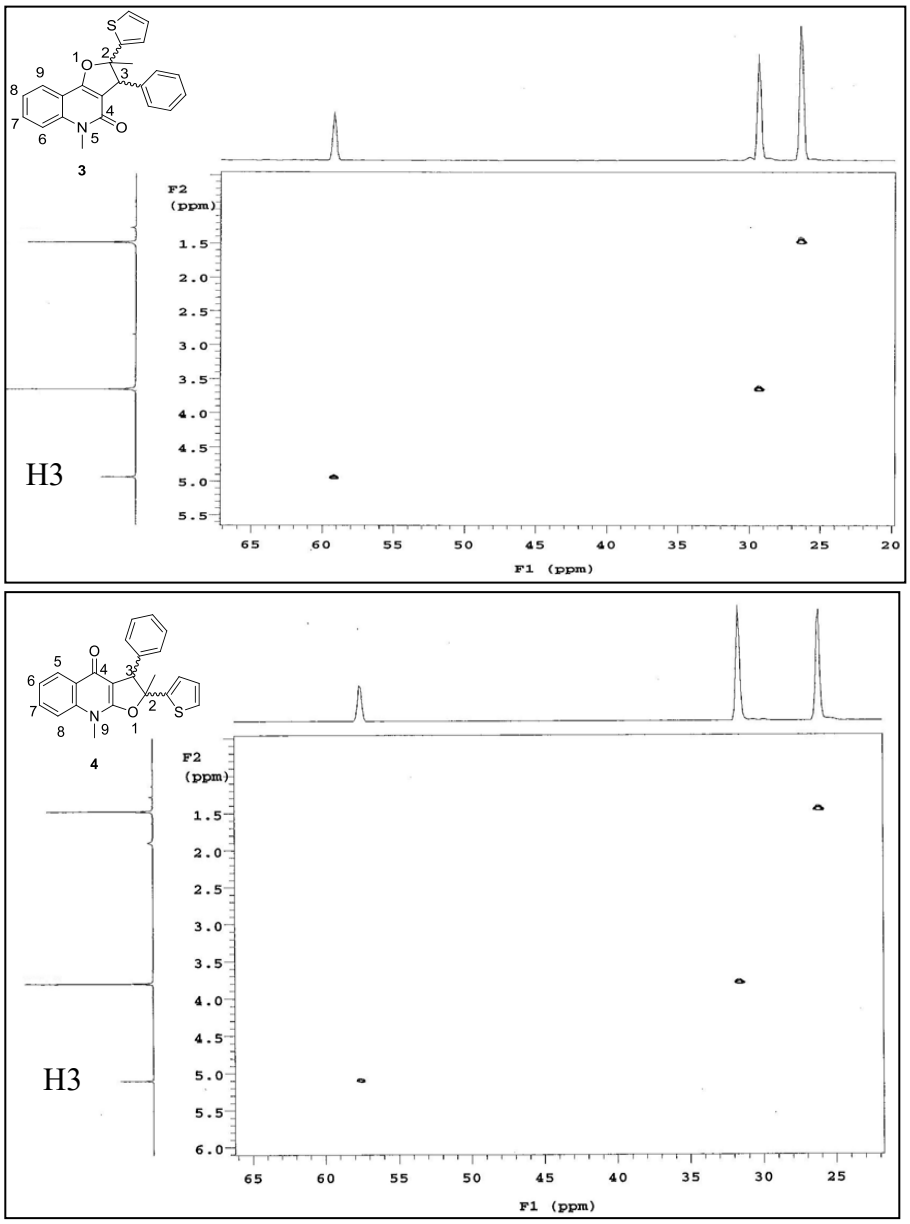

FIGURE 5. HSQC spectra of **3** and **4**.

In our previous work, linear products were not obtained in the reactions of 4-hydroxyquinolinone derivatives with non-heteroaromatic alkenes in the presence of manganese(III) acetate [7]. Although Parsons [6] reported the angular and linear dihydrofuroquinolinones from the reactions of 1,1-disubstituted alkenes, the reaction conditions (heat at 60 ^{0}C in an ultrasonic bath in the presence of $KMnO_4$ as the co-oxidant) and alkene (1,1,2-trisubstituted and heteroaromatic alkene) are different from this study. Therefore, it is obvious that the cyclization is prone to occur at the enolic keto carbonyl group in the cation **D** and a thermodynamically more stable angular product **3** would be produced more then linear product **4** (Fig. 6).

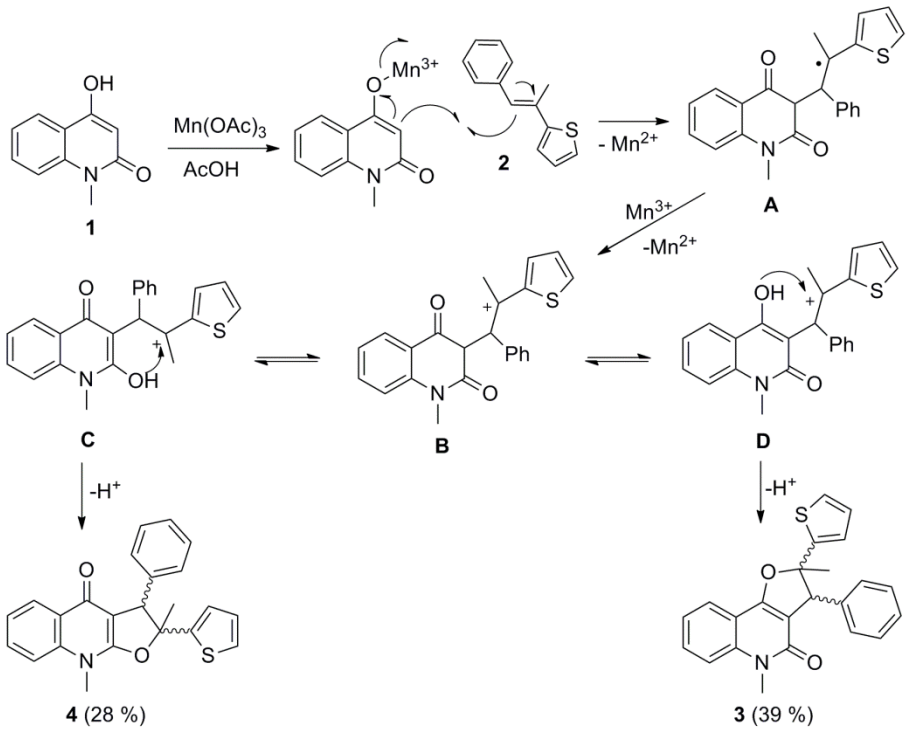

FIGURE 6. Proposed mechanism for the formation of dihydrofuroquinolinones.

4. CONCLUSION

In conclusion, angular dihydrofuroquinolinone **3** (3%) and linear dihydrofuroquinolinone **4** (28%) were synthesized as a result of the cyclization reaction of 4-hydroxy-1-methyl-2*H*-quinoline-2-one (**1**) with (E)-2-(1-phenylprop-1-en-2-yl) thiophene (**2**) via $Mn(OAc)_3$. We have synthesized thienyl substituted dihydrofuroquinolinone derivatives, which have biological activity potential. The reaction mechanism was proposed for the formation of these products.

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ÖZET

Açısal (**3**) ve çizgisel (**4**) dihidrofurokinolinon türevi, mangan(III) asetat varlığında 4-hidroksi-1-metil-kinolin-2-on (**1**) ile (E)-2-(1-fenilprop-1-en-2-il)tiyofen (**2**) nin tepkimesinden elde edildi. Bileşiklerin yapısı, MS, FTIR, ID ve 2D NMR teknikleri kullanılarak aydınlatıldı. Muhtemel bir tepkime mekanizması önerildi.

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