Commun.Fac.Sci.Univ.Ank.Series B
Volume 60, Number 1, Pages 17-24(2018)
DOI: 10.1501/commub_0000000557
ISSN 1303-6017
http://communications.science.ankara.edu.tr/index.php?series=B

SYNTHESES OF NEW POLYSUBSTITUED DIHYDROFURANS MEDIATED BY MANGANESE(III) ACETATE

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Abstract. Efficient syntheses of new 4-(hydroxymethyl)-5,5-dimethyl-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carbonitrile (**3a**) and 4-(hydroxymethyl)-5,5-dimethyl-2-phenyl-4,5-dihydrofuran-3-carbonitrile (**3b**) were achieved via oxidative addition and cyclization reaction of 3-oxo-3-(thiophen-2-yl)propanenitrile (**1a**) and 3-oxo-3-phenylpropanenitrile (**1b**) with 3-methylbut-2-en-1-ol (**2a**) in the presence of manganese(III) acetate. The structures of the compounds (**3a** and **3b**) were determined on the basis of spectral data (IR, NMR and MS). All spectral data are in good agreement with the proposed structures of compounds.

1. Introduction

Dihydrofurans are an important scaffold that occupies a prominent place in the organic syntheses, as they are present in biologically active synthetic molecules and in a wide variety of naturally occurring compounds [1,2]. Their syntheses by the radical cyclization reaction of active methylene compounds with unsaturated systems via transmetal salts (Mn^{3+}, Ce^{4+}, Cu^{2+}) is one of the best method [3-14]. Our research group was interested in preparing of dihydrofurans by manganese(III) acetate have shown antifungal and antibacterial activity [15,16] (Fig. 1) .

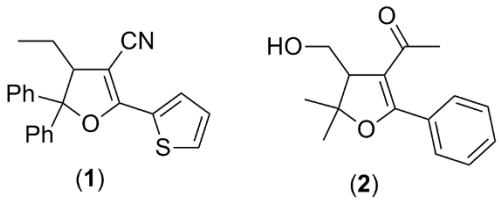

Figure 1. The compounds have antimicrobial activity synthesized in our previous work.

Received by the editors: November 11, 2017; Accepted: August 15, 2018.
Key word and phrases: Manganese(III) acetate, 3-Oxopropanenitrile, Unsaturated alcohol, Dihydrofuran, Radical Cyclization.

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In continuation of our previous work, we have synthesized highly functionalized new dihydrofurans from the reaction of unsaturated alcohol with 3-oxopropanenitriles. Thus, we would like to report a biologically interesting dihydrofurans (**3a** and **3b**) by the mediated of Mn(III) acetate in moderate yields. For this purpose, 3-oxo-3-(thiophen-2-yl)propanenitrile (**1a**) and 3-oxo-3-phenylpropanenitrile (**1b**) were used as active methylene compounds and 3-methylbut-2-en-1-ol (**2a**) were used as an unsaturated alcohol.

2. Materials And Methods

2.1. 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. 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).

2.2. Materials used for syntheses

3-Methylbut-2-en-1-ol (**2a**) is available as commercial product and 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].

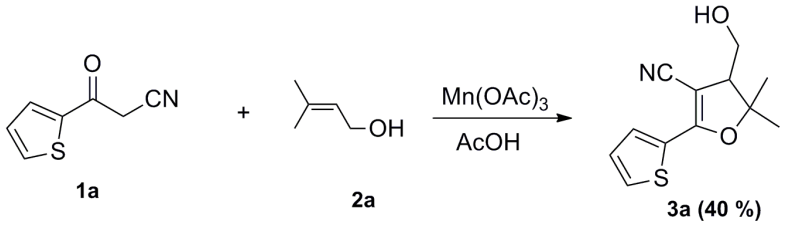
2.3. Syntheses

*2.3.1. General Procedure for the syntheses of the new compounds (**3a** and **3b**)*

A solution of $Mn(OAc)_3{\cdot}2H_2O$ in glacial AcOH was heated under N_2 at 80 °C until it dissolved. Then a solution of a solution of **1a** or **1b** (2 mmol) and unsaturated alcohol **2a** (1 mmol) in 5 mL glacial AcOH was added to the mixture at 80 °C. The reaction was complete when the dark brown colour of the solution disappeared. H_2O was added to the mixture, which was extracted with $CHCl_3$ (3Ł20 mL). The combined organic layers were neutralized with saturated $NaHCO_3$ solution, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to give an oil. The products

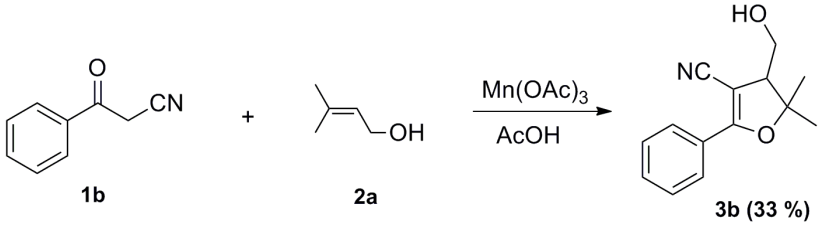
were purified by cc on silica gel or preparative TLC on silica gel, eluating with hexane: AcOEt (2:1) mixtures.

*2.3.1.1. 4-(Hydroxymethyl)-5,5-dimethyl-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carbonitrile (**3a**)*



Light yellow oil; yield 40 %; **IR** ($\nu_{max,}$ KBr): 3445 (OH), 3038 (Ar-H), 2965 (R-H), 2199 (CN). **^{1}H-NMR** ($CDCl_3$), δ (ppm): 1.52 (3H, s, CH_3), 1.54 (3H, s, CH_3), 2.16 (1H, s, OH), 3.11 (1H, dd, J = 7.6 ; 4.8 Hz, CH), 3.83 (1H, dd, J = 11.2; 7.6 Hz, CH_2), 3.90 (1H, dd, J = 11.2, 4.8 Hz, CH_2), 7.12 (1H, dd, J = 5.2, 4.0 Hz, ArH), 7.50 (1H, dd, J = 5.2, 1.2 Hz, ArH), 7.84 (1H, dd, J = 4.0, 1.2 Hz, ArH). **^{13}C NMR** ($CDCl_3$), δ (ppm): 22.02 (CH_3), 29.51 (CH_3), 54.65 (C4), 61.38 (CH_2), 78.67 (C5), 90.95 (C3), 117.93 (CN), 128.22 (CH), 130.00 (CH), 130.29 (CH), 130.84 (C), 162.08 (C2). **LC/MS** m/z: (%): 236 (MH^+, 100).

*2.3.1.2. 4-(Hydroxymethyl)-5,5-dimethyl-2-phenyl-4,5-dihydrofuran-3-carbonitrile (**3b**)*



Light yellow oil; yield 33 %; **IR** ($\nu_{max,}$ KBr): 3438 (OH), 3042 (Ar-H), 2972 (R-H), 2204 (CN). **^{1}H-NMR** ($CDCl_3$), δ (ppm): 1.53 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.96 (1H, s, OH), 3.12 (1H, dd, J = 7.2; 4.4 Hz, CH), 3.85 (1H, dd, J = 11.2; 7.2 Hz, CH_2), 3.93 (1H, dd, J = 11.2, 4.4 Hz, CH_2), 7.41-7.48 (3H, m, ArH), 7.93-7.95 (2H, m, ArH). **^{13}C NMR** ($CDCl_3$), δ (ppm): 22.03 (CH_3), 29.58 (CH_3), 54.82 (C4), 61.38 (CH_2), 80.10 (C5), 89.90 (C3), 118.25 (CN), 127.44 (CH*2), 128.50 (C), 128.85 (CH*2), 131.72 (CH), 166.93 (C2). **GC/MS** m/z: (%): 229 (M^+, 100).

3. Results And Discussion

First, the starting material 3-oxo-3-(thiophen-2-yl)propanenitrile (**1a**) and 3-oxo-3-phenylpropanenitrile (**1b**) were synthesized according to the published procedure [18]. Then, the radical cyclization of 3-oxopropanenitriles (**1a**, **b**) with 3-methylbut-2-en-1-ol (**2a**) were performed in AcOH solution in the presence of manganese(III) acetate at 80 °C in 30 minutes under nitrogen atmosphere using 2:1:3 molar ratio (**1**: **2**: $Mn(OAc)_3$, respectively) (Fig. 2). After the work-up procedure, dihydrofurans (**3a** and **3b**) were purified by column chromatography or preparative TLC and characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS.

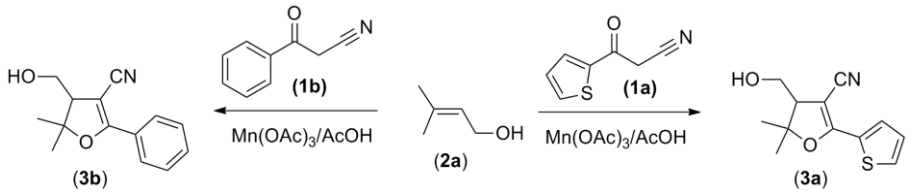


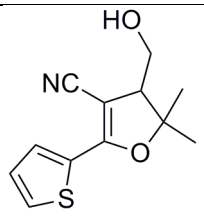
Figure 2. Reaction of 1a, b with 2a.

When the IR spectra of the compounds (**3a-b**) were examined, the OH ($\nu = 3440 cm^{-1}$) and CN ($\nu = 2200\ cm^{-1}$) peaks were observed. ^{1}H NMR spectra of the compounds are similar. Methyl group protons resonated at around 1.5 ppm. H4 proton and methylene ($\underline{CH_2}$-OH) protons resonated at about 3.1 and 3.8-3.9 ppm, respectively. These methylene protons are diastereotopic and the coupling constant of these protons is $^2J_{H\text{-}H}$ 11.2 Hz. These protons were coupled with H4 and exhibited dd signals. In the ^{13}C NMR spectra, CN groups resonated at 118 ppm (Table 1).

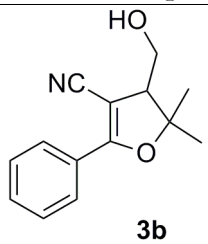
4. Conclusion

Manganese(III) acetate mediated radical addition-cyclization reactions of 3-oxopropanenitriles (**1a**, **b**) and unsaturated alcohol (**2a**) were carried out. We have synthesized new 4-(hydroxymethyl)-5,5-dimethyl-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carbonitrile (**3a**) and 4-(hydroxymethyl)-5,5-dimethyl-2-phenyl-4,5-dihydrofuran-3-carbonitrile (**3b**) compounds by 40% and 33%, respectively. The structures of **3a**, **b** were identified by spectroscopic methods (IR, MS, ^{1}H NMR and ^{13}C NMR). Besides, the products have the biological activity potential owing to the containing hydroxymethyl and cyano moiety.

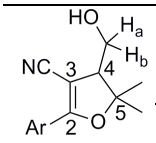
TABLE 1. NMR chemical shifts of enumerated atoms and groups of 3a and 3b



3a



3b



Atom numbers and groups

Compound	^{1}H-NMR (δ) 4	CH_2 (H_a/H_b)	CH_3	^{13}C-NMR (δ) 2	3	4	5	CN	CH_2	CH_3
3a	3.11	3.83/3.90	1.52 1.54	162.08	90.95	54.65	78.67	117.93	61.38	22.02 29.51
3b	3.12	3.85/3.93	1.53 1.55	166.93	89.90	54.82	80.10	118.25	61.38	22.03 29.58

ACKNOWLEDGEMENT. The authors are indebted to the Ankara University BAP (13B4240002) for financial support.

ÖZET

Mangan(III) asetat varlığında, 3-oksopropannitrillerin (1a ve 1b) doymamış alkol (2a) ile radikalik katılma ve halkalaşma reaksiyonu aracılığında yeni 4-hidroksimetil-5,5-dimetil-2-tiyofen-2-il-4,5-dihidrofuran-3-karbonitril (3a) ve 4-hidroksimetil-5,5-dimetil-2-fenil-4,5-dihidrofuran-3-karbonitril (3b) bileşiklerinin etkili sentezi gerçekleştirildi. Bileşiklerin yapısı, MS, FTIR, NMR teknikleri kullanılarak aydınlatıldı. Tüm spektroskopik veriler, önerilen bileşiklerin yapıları ile uyum içerisindedir.

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