International Research Journal of Applied and Basic Sciences
© 2014 Available online at www.irjabs.com
ISSN 2251-838X / Vol, 8 (10): 1733-1736
Science Explorer Publications

Synthesis of Some New Derivatives of 4*H*-Pyran- 4-One

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ABSTRACT: Two different Products were obtained from reactions of 2,6-bis(bromomethyl)-4-oxo-4*H*-pyran-3,5-dicarboxylic acid diethyl ester(5) and KSCN depend on their mole ratio : 2,6-bis(thiocyanatomethyl) (6) and 2,6-bis(isothiocyanatomethyl) (7) derivatives . 2,6-Bis (aminomethyl) (8) was prepared by treatment of 5 with KOCN followed by hydrolysis. 2,6-Bis(azidomethyl) (9) synthesized by means of reaction of 5 with NaN_3 . Treatment of 4-pyrone (4) with excess Bromine led to 2-dibromomethyl-6-tribromomethyl-4-oxo-4*H*-pyran-3,5-dicarboxylic acid diethylester (10).
Keywords: 4-pyrone; thiocyanate; azide; amine; isothiocyanate

INTRODUCTION

4-Pyrones and corresponding derivatives have been the much research due to their importance in various applications and their biological and pharmacological activities .For example some of 4-Pyrones used for treatment of Asthma and allergies and some of these compounds used as herbicides and fungicides [1-5].

Because thiocyanate and isothiocyanate and azide are suitable groups for cycloaddition reactions, we synthesized these derivatives of 4-pyrone from compound (5) which was prepared in five steps according to literatures[6-10] . When two or three Br are present on one carbon atom of a molecule ,this position is ready to hydrolysis and synthesis of new acid and aldehyde ,thus we atemped to preparation of compound 10 .

MATERIALS AND METHODS

General procedure

Melting points were determined with an Electro thermal Instrument model 9100 and are uncorrected. Infrared (IR) spectra were run on a Shimadzu FT-IR 4300

Spectrophotometer as KBr disks or as smears between salt plates. The ^{1}HNMR spectra were recorded on a Varian 300 MHz spectrometer. The ^{13}C NMR spectra were determined on a FT-NMR Brucker 100 MHz spectrometer. Chemical shifts (δ) were reported in values in ppm with TMS as internal standard. Mass spectra were taken with a Shimadzu MS-QP 1100 EX mass spectrometer. Elemental analyses were performed on a Heareus, CHN-O-RAPID analyzer. Solvents were purified and dried where necessary using literature methods. All used chemical reagents in this work were Merck and Fluka marked.

Synthesis of the compounds and spectroscopic structure assignment

2,6-Bis(thiocyanatomethyl)-4-oxo-4*H*-pyran-3,5-dicarboxylic acid diethyl ester (6) . 0.14 gr. (0.33 mmole) of 5 in CH3CN was stirred with 0.06 gr. (0.66 mmole) of KSCN at room temperature for 15 minutes. Precipitate KBr was filtered and filtrate was evaporated to yield an oil which Was crystallized from CH_3CN-H_2O as shining white crystals, 0.11 gr.(91.6%), mp. 99.8 °C ; Ir. : 1279(C=C),1641(C=O 4- pyrone) , 1749(C=O ester) , 2156(C≡N) Cm^{-1}; ^{1}HNMR($CDCl_3$) : δ 1.3 (t,6H, -CH_3) , 4.3 (s,4H, -CH_2S) , 4.4 (q,4H, -CH_2 ester); ^{13}C NMR ($CDCl_3$) δ 13.7, 35.5, 59.6, 108, 112, 165, 180, 187; ms: m/z 382(m^+ , 70),337(45) , 324(50) , 290(75) , 278(100) , 250(98) , 234(90) , 191(30) , 166(20) , 96(45) , 66(97) , 43.1(24) . Anal.Calc. for $C_{15}H_{14}N_2O_6S_2$: C,47.11; H,3.69; N,7.33; S,16.77. Found: C, 47.10 ; H,3.70; N,7.31; S,16.75;

2,6-Bis(isothicyanatomethyl)-4-oxo-4*H*-pyran-3,5-dicarboxylicacid diethyl ester (7) . 0.14 gr. (0.33 mmole) of 5 in 5 ml of CH_3CN was stirred with 0.03 gr. (0.33 mmole) of KSCN at room temperature for 30 minutes. After filtration of formed KBr , solvent was evaporated to yield an oil which crystallized from CH_2Cl_2-Heptane as lemon crystals, 0.09 gr. (75%) , mp. 118.5 °C ; ir(KBr) : 1279(C=C),1641(C=O 4- pyrone) , 1749(C=O ester) , 2000-2400 (N=C=S) Cm^{-1}; ^{1}HNMR($CDCl_3$) : δ 1.4 (t,6H,-CH_3) , 4.4 (s,4H,-CH_2N) , 4.5 (q,4H, -CH_2 ester); ^{13}C NMR ($CDCl_3$) δ 13.7, 46.8, 59.6, 108.3, 155, 165, 180, 187; ms: m/z 382(m+ ,

70),337(45) , 324(50) , 290(75) , 278(100) , 250(98) , 234(90) , 191(30) , 166(20) , 96(45) , 66(97) , 43.1(24) . Anal.Calc. for $C_{15}H_{14}N_2O_6S_2$: C,47.11; H,3.69; N,7.33; S,16.77. Found: C,47.12; H,3.68;N,7.32 ; S, 16.78;

2,6-Bis(aminomethyl)-4-oxo-4*H*-pyran-3,5-dicarboxylicacid diethyl ester (8) . 0.20 gr. (0.47 mmole) of 5 in 5 ml of CH_3CN and 1 ml of water was stirred with 0.08 gr. (0.94 mmole) of KOCN at room temperature for 60 minutes. The organic product was extracted with toluene. The toluene was dried (magnesium sulfate) and evaporated to yield to pink crystals, 0.07 gr. (50%) , mp. 96.5 °C ; ir (KBr) : 1279(C=C),1641(C=O 4- pyrone) , 1749(C=O ester) ,3408,3410(N-H) Cm^{-1} ; ^{1}HNMR ($CDCl_3$): δ 1.3 (t,6H) , 2.2(H of N-H), 4.2 (s,4H) , 4.4 (q,4H); ^{13}C NMR ($CDCl_3$) δ 13.7, 43.8, 59.6, 107, 165, 181, 187; ms: m/z 301(10), 257(10), 149(10) , 110(10) , 99(20) , 85(30) , 71(42) , 57(63),44(100) . Anal.Calc. for $C_{13}H_{18}N_2O_6$: C,52.34; H,6.08; N,9.39;. Found: C,52.30; H,6.06;N,9.40 ;

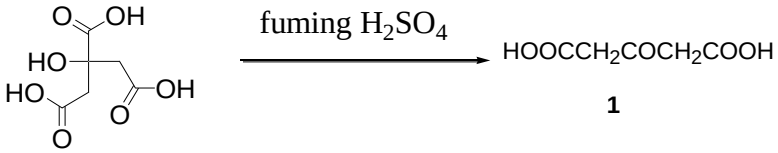
2,6-Bis(azidomethyl)-4-oxo-4*H*-pyran-3,5-dicarboxylicacid diethyl ester (9) . 0.14 gr. (0.33 mmole) of 5 was stirred in 5 ml of methanol with 0.05 gr. (0.66 mmole) of NaN_3 at room temperature for 10 minutes. 5 ml of water was added to the solution quickly. The resultant product was filtered. The toluene was filtered and dissolved in 10 ml of CHCl3. The chloroform was dried (magnesium sulfate) and evaporated to yield an oil which was crystallized from methanol-water as red-brown crystals, 0.09 gr. (78.2%) , mp. 126 °C ; ir (KBr) : 1279(C=C),1641(C=O4-pyrone 4-pyrone) , 1749(C=O ester) ,2120(N=N) Cm^{-1} ; ^{1}HNMR (CDCN): δ 1.3 (t,6H,-CH_3), 4.4 (s,4H,-CH_2N) , 4.5 (q,4H, -CH_2 ester); ^{13}C NMR (CDCN) δ 13.7, 51, 59.6, 108, 112, 165, 180, 187; ms: m/z 267(10), 222(10), 193(18) , 153(18) , 123(22) , 96(60) , 55(95) , 43(100),42(45) . Anal.Calc. for $C_{13}H_{14}N_6O_6$: C,44.57; H, 4.03; N, 23.99;. Found: C,44.60 ; H,4.02;N, 24.0 ;

Dibromomethyl-6-tribromomethyl-4-oxo-4*H*-pyrane-3,5-dicarboxylic acid diethyl ester (10). 7.27 gr.(27.1 mmole) of pyrone (4) was refluxed in a 250 ml flask in 200 ml of CH2Cl2 for 30 minutes. A solution of 11.9 gr.(48.5 mmole) of bromine in 150 ml of CH2Cl2 slowly added to it over to period of 2 hours. After the addition was completed the solution was refluxed for 1.5 hours, then was allowed to cool to room temperature. The solution was then washed with sodium bicarbonate solution and filtered. The organic layer was separated, dried (magnesium sulfate) and solvent was evaporated. The residue was separated by column chromatography (silica gel-ethyl acetate – petroleum ether) to give 11 and12 in 80.2 % and 10% yield, respectively. We could not to perform purification of compound (12), we don't present spectral specifications for it in this paper. Compound (10) was obtained as white square pyramidal crystals,mp.158 °C (with decomposition) ; ir (KBr): 716(C-Br) ,1279(C=C),1641(C=O 4-pyrone) , 1749(C=O ester) Cm^{-1} ; 1Hnmr (CDCl3): δ 1.35 (t,6H,-CH_3), 4.45 (q,4H, -CH_2 ester) , 6.75 (s,1H,-$CHBr_2$); ^{13}C NMR (CDCl3) δ 13.7, 22,44, 59.6, 111, 165, 181, 187; ms: m/z 537(10), 506(18), 504(35) , 456(30) , 412(25) , 400(8), 348(20), 320(15), 268(70)44(70). Anal.Calc. for $C_{13}H_{11}Br_5O_6$: C,23.53; H, 1.67;. Found: C, 23.48; H,1.70 ;

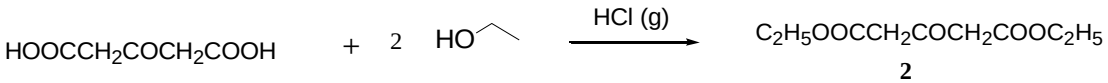
RESULTS AND DISCUSSION

Steps of preparation of 2,6- bis(bromomethyl)- derivative

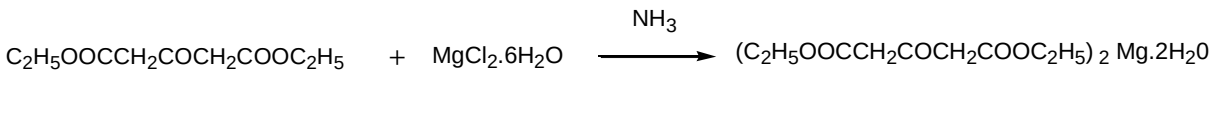
Primairely, we were synthesized 2,6-bis(bromomethy)-4-oxo-4*H*-pyran-3,5-dicarboxylic acid diethyl ester (5) as shown in schemes1-5.



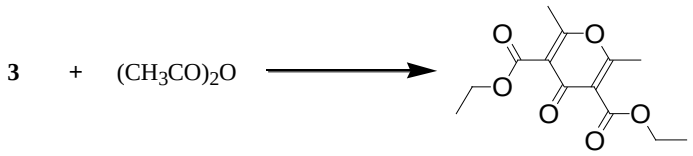
Scheme 1: Preparation of acetone dicarboxylic acid.



Scheme 2: Esterification reaction of 1.

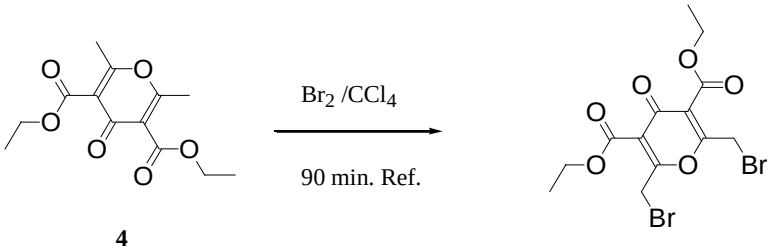


Scheme 3: Preparation of magnesium complex of 2.



4

Scheme 4: Synthesis of 4-pyrone (4)

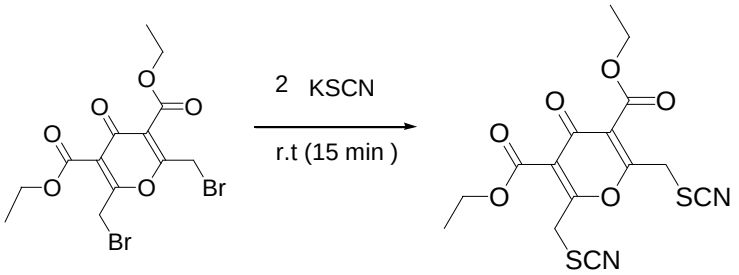


4 **5**

Scheme 5: Bromination of 4-pyrone

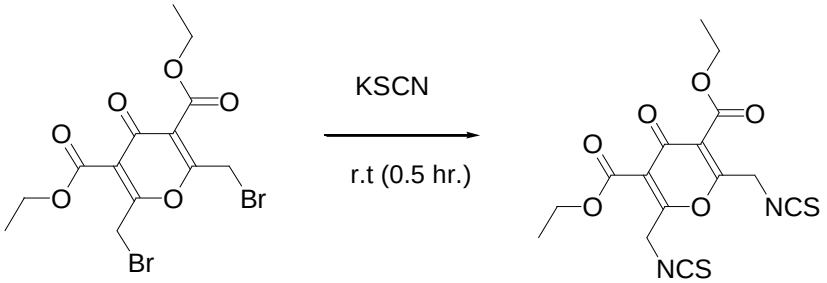
Two different products obtain from same reaction

Compound (5) was treated with KSCN in CH_3CN to give products 6,7 in 91.6% and 75.0% yields, respectively (schemes 6,7).



5 **6**

Scheme 6: The substance/reagent ratio is 2:1.

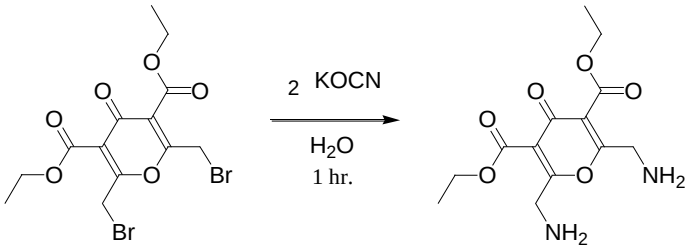


5 **7**

Scheme 7: The substance/reagent ratio is 1:1.

As proved of schemes 6 and 7, when 5 reacts with 1 mole of KSCN , Thiocyanate ion attacks of N – side. On the other hand, when 5 reacts with 2 mole of KSCN, Thiocyanate ion attacks of S –side. Our purpose of means of reaction 1 was synthesis of 2-bromomethyl-6-thiocyanatomethyl-4-oxo-4*H*-pyrane-3,5-dicarboxylic acid diethyl ester but ^{1}Hnmr,ir and mass spectroscopic methods show that our new compound is 7.

The reaction of 5 with KOCN in CH_3CN and in the presence of water at room temperature gave 8 in 50% yield (scheme 8) .

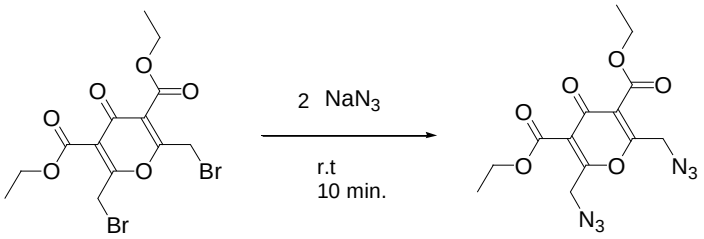


5 8

Scheme 8: Synthesis of amine through cyanate

In the case of reaction 5 with KOCN, cyanate ion only attacks from N- side and it never attacks from O-side, and this matter is independent of substance/reagent mole ratios. 2,6-BIS (isocyanatomethyl)-4-oxo-4*H*-pyrane –3,5-dicarboxylic acid diethyl ester forms as intermediate of this reaction but it reacts with H_2O and convert to amine 8. Unfortunately we could not trap this compound.

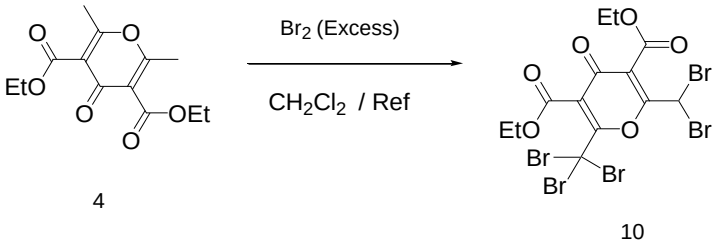
Structure of 1º aliphatic amine 8 was established by formation of light green colure with $CuSO_4$ solution, in addition to spectroscopic methods [11] .



5 9

Scheme 9: Synthesis of azide derivative.

Treatment of NaN_3 with 5 in methanol gave 9 in 78.2% yield (scheme 9) .



4 10

Scheme 10: Preparation of new product from bromination of 4-pyrone (4).

Bromination of 4-pyrone (4) with excess bromine in CH_2Cl_2 led to 10 in 81% yield and a trace by- product which instead of our tries did not obtain as pure substance (scheme 10); therefor we could not estblish its structure.

ACKNOWLEDGEMENTS

Financial support of this work by Tabriz University Research Council is gratefully acknowledged.

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