SYNTHESIS OF NEW 2-ARYL-4*H*-4-OXO-1-BENZOPYRAN OXIME ETHERS

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Abstract : Synthesis of 2-(5-formyl-2-thienyl)-4*H*-1-benzopyran-4-one and a series of five 4*H*-1-benzopyran-4-one-2-(phenyl or thienyl) aldoxime ethers is reported.

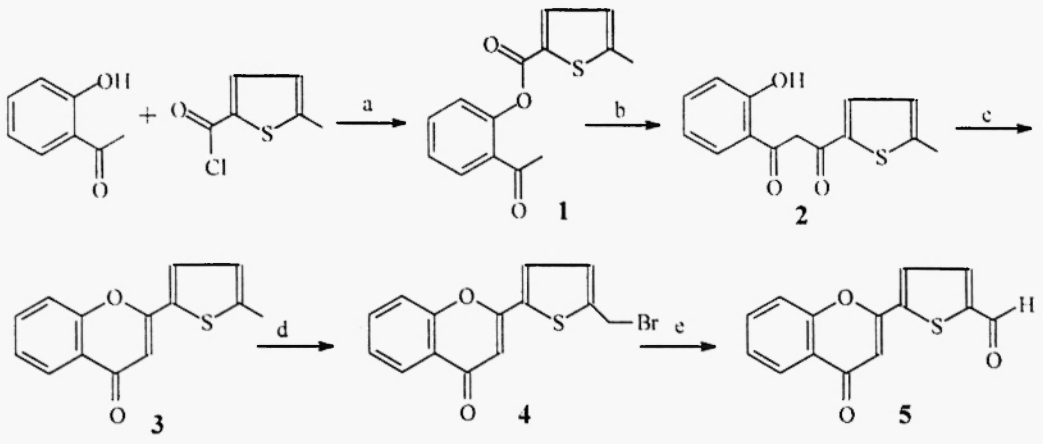
Introduction

Oximes and their *O*-alkyl ethers are found in the structure of many drugs such as the antibacterials aztreonam, cefotaxime, ceftizoxime, and cefuroxime, the antifungal oxiconazole, the antidepressant fluvoxamine, and the antidote pralidoxime for therapy of organophosphate poisoning (1). Oximes are often used for molecular modification of new potential drugs. In particular, the antimicrobial activity of oximes has received much attention. The oxime-ether derivatives of erythromycin (2), enviroxime and its C-2 analogs (3) are selective antiviral drug candidates against both rhinoviruses and enteroviruses. Potent antifungal activities of some new flavonyl oxime ethers (4,5) and ethylideneaminoxymethyl-substituted dioxalones (6) have been reported. Bis-amidoximes and bis-*O*-alkylamidoximes have been studied as prodrugs for active anti-*Pneumocytis carinii* compounds (7). In this study, we report the synthesis and isomeric character of some new 2-(phenyl or thienyl)-4*H*-1-benzopyran-4-one aldoxime ethers.

Results and Discussion

For the synthesis of 2-(5-formyl-2-thienyl)-4*H*-1-benzopyran-4-one (**5,** Scheme 1), the Baker-Venkataraman (8) rearrangement, a general procedure for the preparation of flavones, was chosen. The first step involves conversion of 2'-hydroxyacetophenone into 5-methyl-2-thiophenecarboxylic acid 2'-acetyl-phenyl ester **1**. The ester was treated with KOH/pyridine to form the corresponding 1,3-diketone **2**. Intramolecular dehydration of this diketone with anhydrous sodium acetate in glacial acetic acid gave the 2-(5-methyl-2-thienyl)-4*H*-1-benzopyran-4-one **3**. This compound was converted into bromomethyl derivative **4** by reaction with *N*-bromosuccinimide in the presence of benzoyl peroxide. Treatment of **4** with hexamethylenetetramine in glacial acetic acid gave 2-(5-formyl-2-thienyl)-4*H*-1-benzopyran-4-one **5.** Aldehydes **5**, 7(9), **8**(10), were allowed to react with *O*-benzylhydroxylamine.HCl in the presence of pyridine to give the oximes **6, 10-11** (Scheme 2). In a similar reaction, we were successful in obtaining from **9**(11) the *O*-benzyloxime **12** and the *O*-(2-dimethylaminoethyl)oxime **13**. We were unable to isolate

Scheme 1



a : Pyridine, b : Pyridine /powdered KOH, c : Anhydrous CH_3COONa / CH_3COOH, d : NBS, e : Hexa-methylenetetramine / HCl

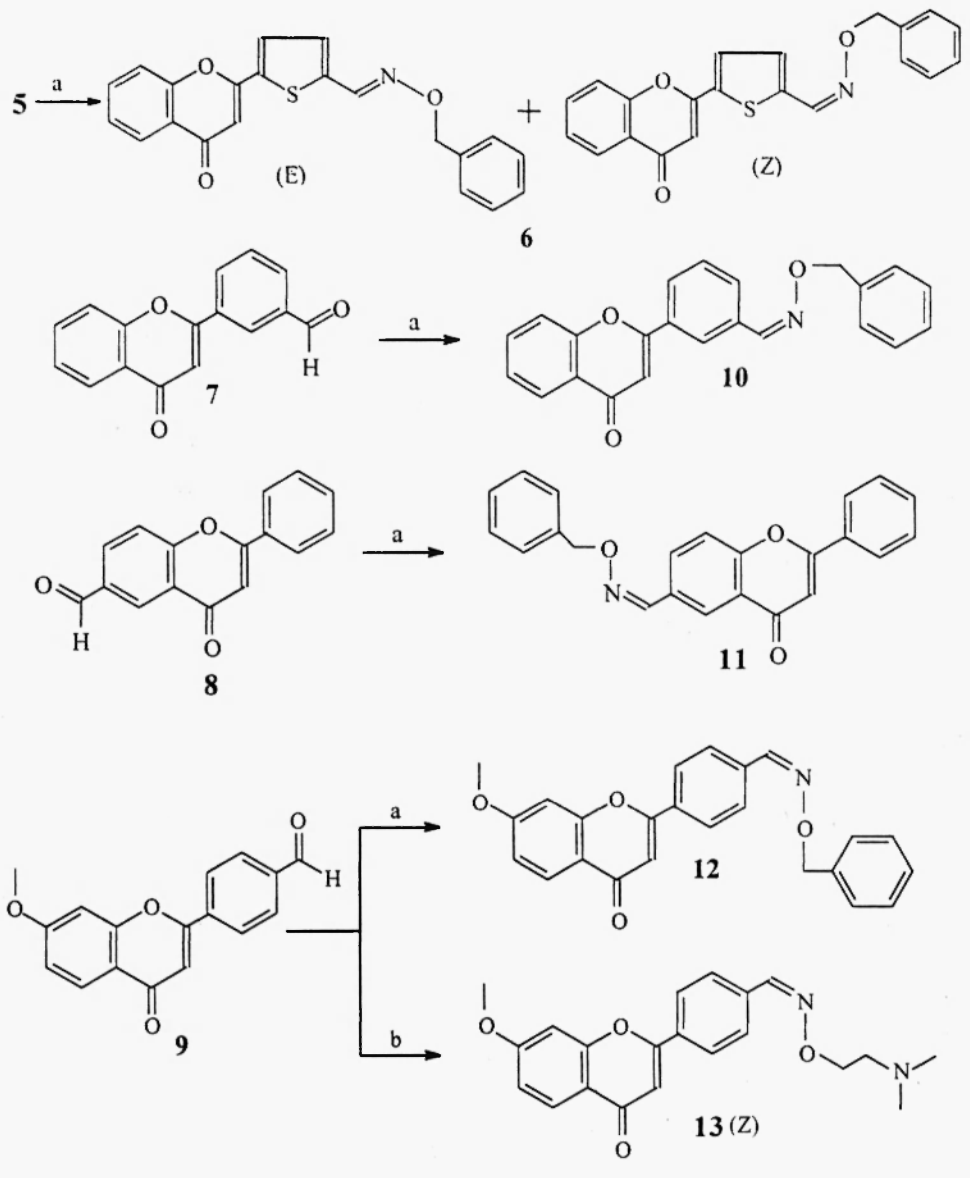
the *O*-(2-dimethylaminoethyl)oxime from **5**. Generally, oxime ethers show geometric (E/Z) isomerism and their ^{1}H-NMR spectra can be used to demonstrate that mixtures are formed. Previously published NMR studies have showed that C=N-O-CH_2 protons signal for the E isomer occurs downfield from that of the Z isomer (12). For example, in a series of flavonecarboxyaldehyde–[O-(2-dimethylaminoethyl)-oxime] derivatives the E isomer OCH_2 signal appears at δ 4.35-4.45 ppm and the Z isomer values are at δ 4.20-4.30 ppm (4). Only one isomer of compound **13** was obtained and the C=N-O-CH_2 protons signal was observed at δ 4.25 ppm ; perhaps this represents the Z isomer but in the absence of data for the other isomer, rigorous assignment cannot be made. For compounds **10-12** only one oxime isomer was isolated and all showed C=N-O-CH_2 signals at δ 5.20 ± 0.05 ppm. We do not have sufficient data to make E/Z assignments. Compound 6 exists as a mixture of Z/E isomers, as indicated by two signals for both the C=N-O-CH_2 and CH=N protons. The methylene protons gave two singlets at δ 5.18 and 5.36 ppm (integrated intensity ratio of 1:3) and the methine proton appeared at δ 8.09 and 8.57 ppm (integrated intensity ratio of 3:1). Thin layer chromatography analysis (EtOAc / *n*-hexane 35:65) of the mixture is in agreement with the NMR data as evidenced by two spots with very close Rf values (0.6 / 0.55).

Biological evaluation of the synthesized compounds is under investigation.

Experimental

Uncorrected melting points were measured on a Mel Temp 3.0 capillary melting point apparatus. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian GX400 spectrometer in DMSO-d_6, chemical shifts (δ) are in ppm relative to TMS, and coupling constants (J) are reported in hertz. The EI mass spectra were obtained with a VG Platform II spectrometer by TUBITAK (Instrumental analyse Lab. Ankara/Turkey). Microanalyses were performed by Atlantic Microlab Inc, (Norcross, GA).

Scheme 2



a : *O*-benzylhydroxylamine.HCl b : *O*-(2-dimethylaminoethyl)hydroxylamine . 2HCl

2'-Acetylphenyl 5-methyl-2-thiophenecarboxylate (1)

5-Methyl-2-thiophenecarboxylic acid (8g, 56.3 mmol) in 50 ml of $SOCl_2$ was heated at reflux for 2h and then excess reagent was evaporated under reduced pressure. *o*-Hydroxyacetophenone (7.65 g, 56.3 mmol) and 20 ml of pyridine were added to the residue and the mixture was heated for 0.5 h at 80°C. The mixture was cooled and poured into ice-water, acidified with HCl, and the resulting precipitate was filtered and washed with water. Crystallization from EtOH gave **1** (12.7 g, 86.8 %), as white crystals, mp 110-112 °C. Anal. Calcd. for $C_{14}H_{12}O_3S$: C, 64.60 ; H,4.65 ; S, 12.32. Found : C, 64.55; H, 4.64 ; S, 12.16.

1-(2-Hydroxyphenyl)-3-(5-methyl-2-thienyl)-1,3-propanedione (2)

A mixture of **1** (5.5 g, 21.2 mmol) pyridine (40 ml) and powdered KOH (2 g) was stirred for 1h at 60°C and then cooled, treated with water, and the solution pH adjusted to 5 with HCl. The yellow precipitate was filtered and washed with water. Crystallization from EtOH gave **2** (3.1 g, 56.4 %), as yellow crystals, mp 92-93 °C. Anal. Calcd. for $C_{14}H_{12}O_3S$: C, 64.6 ; H, 4.65 ; S, 12.32. Found : C, 64.74; H, 4.79 ; S, 12.09.

2-(5-Methyl-2-thienyl)-4*H*-1-benzopyran-4-one (3)

A mixture of **2** (3 g, 11.5 mmol) and anhydrous sodium acetate (5g, 61 mmol) in 50 ml of glacial acetic acid was heated at reflux for 4 h. Water was added and the precipitate was collected. Crystallization from EtOH gave **3** (2.4 g, 86.3 %) as white needles, mp 85-6 °C ; ^{1}H-NMR δ 2.5 (s, 3H), 6.7 (d, 1H), 6.95 (s, 1H), 7.42 (td, 1H, J = 8, J = 1.5), 7.6 (d, 1H, J = 8), 7.74 (td, 1H, J = 8, J= 1.5), 7.79 (d, 1H), 7.96 (m, 1H). Anal. Calcd. for $C_{14}H_{10}O_2S$: C, 69.4; H, 4.16 ; S, 13.23. Found : C, 69.35 ; H, 4.33 ; S,12.97.

2-(5-Bromomethyl-2-thienyl)-4*H*-1-benzopyran-4-one (4)

A mixture of **3** (1.25 g, 5.2 mmol), *N*-bromosuccinimide (0.92 g, 5.2 mmol) and a catalytic amount of benzoyl peroxide in CCl_4 (50 ml) was heated under reflux for 6h. The mixture was filtered while hot and CCl_4 was evaporated. Crystallization of the solid residue (EtOAc / *n*-hexane, 30:70, twice) gave white needles, mp 130-131 °C, yield (0.8 g, 48 %) ; ^{1}H-NMR δ 5.25 (s, 2H), 6.92 (s, 1H), 7.38 (d, 1H, J = 6.5), 7.5 (t ,1H, J = 8), 7.64 (d, 1H, J = 8), 7.82 (td, 1H, J= 8, J = 1.3), 7.9 (d, 1H, J = 6.5), 8.2 (dd, 1H, J = 8, J = 1.1). Anal. Calcd. for $C_{14}H_9BrO_2S$: C,52.35 ; H, 2.82 ; S, 9.98. Found : C,52.31 ; H, 2.96 ; S, 10.14.

5-(4*H*-4-oxo-1-benzopyran-2-yl)-2-thiophenecarboxaldehyde (5)

A mixture of **4** (0.78 g, 2.43 mmol) and hexamethylenetetramine (3.5 g, 25 mmol) in 30 ml of acetic acid (50%) was heated at reflux for 2.5 h. HCl (10 ml, 18%) was added and the mixture was heated at reflux for an additional 0.5 h. The mixture was diluted with water and the precipitate was collected. Crystallization of the solid (EtOAc / *n*-hexane, 1 : 1) gave **5** as white powder, mp 178-179 °C, yield (0.36g, 58.1 %) ; ^{1}H-NMR δ 7.15 (s, 1H), 7.51 (t, 1H, J = 8), 7.73 (d, 1H, J = 8), 7.84 (td, 1H, J = 8, J = 1.3), 8.03 (d, 1H, J = 8), 8.13 (d, 1H), 8.19 (dd, 1H), 10.0 (s, 1H). MS *e/z* 256 ($M^{+\cdot}$, 100), 258(5), 227(25), 120(80), 92 (50). Anal. Calcd. for $C_{14}H_8O_3S$.0.25 EtOAc : C, 64.7; H, 3.62 ; S,11.52. Found : C,64.3 ; H, 3.38 ; S, 11.8.

General synthesis of 6, 10-12

A mixture of **5, 7-9** (1 mmol), *O*-benzylhydroxylamine.HCl (0.16g, 1 mmol), pyridine (1ml), and abs. EtOH (10 ml) was heated under reflux for 8 h, then cooled, treated with *n*-hexane and allowed to stand overnight. The precipitate was filtered, dried, washed with water, and dried again. Crystallization of crude product from isopropanol gave pure **10-12**.

5-(4*H*-4-oxo-1-Benzopyran-2-yl)thiophen-2-carboxaldehyde *O*-benzyloxime (6)

The crude product was purified by column chromatography (silica gel) by using a mixture of EtOAc / *n*-hexane (40 : 60) as eluent, mp 128-32 °C, yield (0.15 g, 41.5 %) ; ^{1}H-NMR δ 5.18 and 5.36 (2s, 2H), 6.97 (s, 1H), 7.3-7.55 (m, 6H), 7.65 (m, 2H), 7.81 (t, 1H), 8.05 (m, 2H), 8.09 and 8.57 (2s, 1H). MS *m/z* 361(M^+, 90), 271(2), 254(5), 243(3), 120(13), 91(100). Anal. Calcd. for $C_{21}H_{15}NO_3S$.0.1 HOH : C, 69.44 ; H, 4.22 ; N, 3.85 ; S, 8.82. Found : C; 69.33; H, 4.28 ; N.3.80 : S, 8.57.

3-(4*H*-4-oxo-1-Benzopyran-2-yl)benzaldehyde *O*-benzyloxime (10)

Mp 129 °C, yield (0.19g, 54.5 %) ; ^{1}H-NMR δ 5.25 (s, 2H), 7.05 (s, 1H), 7.3-7.45 (m, 5H), 7.5 (t, 1H, J = 8), 7.62 (td, 1H, J = 8, J = 1.1), 7.78 (d, 1H), 7.85 (m, 2H), 8.05 (d, 1H, J = 8), 8.15 (d, 1H, J = 8), 8.28 (s, 1H), 8.41(s, 1H). ^{13}C-NMR δ 75.7, 107.4, 118.5, 123.3, 124.8, 125.1, 125.6, 127.7, 127.8, 128.3, 128.4, 129.3, 129.7, 131.7, 132.8, 134.4, 137.4, 148.5, 155.6, 161.9, 177. MS *m/z* 355(M^+, 9), 249(2), 219(2), 165(4), 152(3), 121(5), 91(100). Anal. Calcd. for $C_{23}H_{17}NO_3$: C, 77.73 ; H, 4.82 ; N, 3.94. Found : C, 77.56 ; H, 4.86 ; N, 3.95.

2-Phenyl-4*H*-4-oxo-1-benzopyran-6-carboxaldehyde *O*-benzyloxime (11)

Mp 148-9 °C, yield (0.18g, 50.7 %) ; ^{1}H-NMR δ 5.15 (s, 2H), 7.05 (s, 1H), 7.28-7.3 (m, 5H), 7.58 (m, 3H), 7.8 (d, 1H, J= 8.1Hz), 8.0-8.14 (m, 3H), 8.22 (d, 1H), 8.35(s, 1H). ^{13}C-NMR δ 75.8, 107.2, 119.3, 123.4, 123.8, 126.3, 127.7, 128.2, 128.3, 128.9, 129.2, 130.8, 131.4, 131.8, 137.4, 148.1, 155.1, 162.2, 176.3. MS e/z 355(M^+, 26), 249(8), 219(4), 165(5), 152(3), 91(100). Anal. Calcd. for $C_{23}H_{17}NO_3$: C, 77.73 ; H, 4.82; N, 3.94. Found : C, 77.7 ; H, 4.90 ; N, 3.96.

4-(7-Methoxy-4*H*-1-benzopyran-2-yl)benzaldehyde *O*-benzyloxime (12)

Mp 140-2 °C, yield (0.21g, 54.5 %) ; ^{1}H-NMR δ 3.91 (s, 3H), 5.21 (s, 2H), 6.9 (s, 1H), 7.05 (dd, 1H, J = 8, J = 1.1), 7.25-7.45 (m, 6H), 7.78 (d, 2H, J = 8), 7.93 (d, 1H, J = 8), 8.12 (d, 2H, J = 8), 8.39 (s, 1H). ^{13}C-NMR δ 55.9, 75.7, 100.9, 107.1, 114.6, 117.1, 126.1, 126.5, 127.2, 127.8, 128.2, 128.3, 132.2, 134.6, 137.3, 148.4, 157.4, 161.3, 163.9, 176.2. MS *m/z* : 385(M^+ ,1), 295, 251(2), 233(12), 91(100). Anal. Calcd. for $C_{24}H_{19}NO_4$: C, 74.79 ; H, 4.97; N, 3.63. Found : C, 74.75 ; H, 5.02 ; N, 3.65.

4-(7-Methoxy-4*H*-4-oxo-1-benzopyran-2-yl)benzaldehyde *O*-(2-dimethylaminoethyl)oxime (13)

A mixture of **9** (0.28g, 1mmol), and *O*-(2-dimethylaminoethyl)hydroxylamine.2HCl (13) (0.2g, 1.13 mmol) pyridine (1ml), and abs. EtOH (10 ml) was heated under reflux for 10h. The solvent was removed and the resultant solid was stirred in a 10 % K_2CO_3 solution, and the mixture was extracted with chloroform. The organic layer was concentrated and the residue was chromatographed on silica gel using $CHCl_3$ /

isopropanol / NH_3 (25%) , (20 : 5 : 0.1) as an eluent ; mp 90-91 °C, yield (0.2 g, 54.6 %) ; ^{1}H-NMR δ 2.2 (s, 6H), 2.55 (t, 2H), 3.92 (s, 3H), 4.23 (t, 2H, J = 8), 6.9 (s, 1H), 7.05 (dd, 1H, J = 8, J = 1.2), 7.3 (d, 1H, J = 1.2), 7.78 (d, 2H, J = 8), 7.94 (d, 1H, J = 8), 8.12 (d,2H, J = 8), 8.3(s, 1H). ^{13}C-NMR δ 45.3, 55.9, 57.4, 72, 100.9, 107.1, 114.6, 117.1, 126.1, 126.4, 127.2, 132, 134.8, 147.8, 157.4, 161.3, 163.8, 176. MS e/z 366(M^+,1), 277(2), 249(2), 234(3), 208(3), 152(6), 58(100). Anal. Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.84 ; H, 6.05 ; N, 7.65. Found : C, 68.77 ; H, 6.10 ; N, 7.60.

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