Aldol Reactions of γ- and ε-Methylene in 5-Membered Heteroaromatic Compounds

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5-Methyl-2-thiophenecarboxaldehyde (**1a**) and 3-methyl-2-thiophenecarboxaldehyde (**6**) underwent intermolecular aldol reactions in which the methyl group behaved as active methylene in the presence of potassium cyanide. 5-Methylfurfural (**1b**) gave only 5,5'-dimethylfuroin in the presence of potassium cyanide. But **1b** formed an intermolecular aldol reaction product when sodium hydroxide was used.

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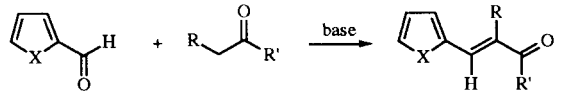
Aldol condensation reactions of heteroaromatic carbonyl compounds have been widely investigated in line with exploring the scope of the reaction as well as examining the reactivities of the heterocyclic compounds. Most reactions of the type in Scheme 1 have been examined and conjugated enone compounds have been isolated in low to moderate yields [1].

Scheme 1



X = O, S, NCH_3

Aldehyde derivatives of heterocyclic compounds undergo, in general, condensation reactions with active α-methylene compounds in the presence of strong bases. Furfural, for example, condensed with acetaldehyde in the presence of sodium hydroxide in 60-91% yield [2]. However, 5-methylfurfural (**1b**) underwent similar condensation in 24% yield [3]. Presence of the methyl group lowered the yield of the reaction, but no reaction in which the methyl group behaved as an active methylene was reported.

5-Methylthiophenecarboxaldehyde (**1a**) and **1b** failed to give condensation reaction products with tetralone or 3,4-dichloroacetophenone [4]. 5-*n*-Propyl- or 5-*n*-heptyl-2-thiophenecarboxaldehyde also did not react with 4-acetylbiphenyl [5]. On the other hand, 3-methyl-2-thiophenecarboxaldehyde (**6**) reacted with acetaldehyde, giving a condensation product in 39% yield [6]. 5-Methyl-2-acetylthiophene underwent condensation reaction with benzaldehyde in the presence of sodium hydroxide producing an enone compound in 82-95% yield [7]. However, the reaction took place at the methyl carbon in the acetyl group, and not in the 5-methyl carbon. There were several cases in which **1b** underwent aldol condensation reactions, but none of them showed the 5-methyl group behaved as an anionic center [8-11]. There has been no report that the methyl protons in furan or thiophene behave as if they are active methylene protons.

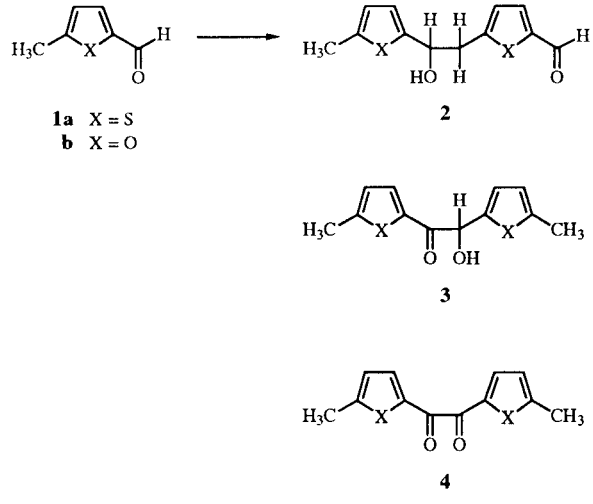
There are a few reports dealing with condensation reactions at the γ-position in conjugated cycloalkenones. For example, 3-methyl-2-cyclohexen-1-one condenses with benzaldehyde at the 3-methyl group only [12].

In the course of our extensive investigation on the benzoin condensation reaction of heterocyclic aldehydes we came to isolate an aldol-type adduct (**2a**) from the reaction of 5-methyl-2-thiophenecarboxaldehyde (**1a**). We report the unusual results here in detail.

Results and Discussion.

When **1a** was refluxed with potassium cyanide in ethanol-water and the reaction mixture was chromatographed on a silica gel column with benzene, **3a** (10%) and **4a** (20%) were isolated (Scheme 2) [13]. But there was additional gummy material (*ca.* 30%) which did not solidify upon treatment with various solvents or upon

Scheme 2



1a X = S
b X = O

2

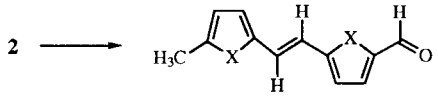
3

4

leaving in a refrigerator for a long period of time (2-3 months). The gummy material was rechromatographed twice until it was pure enough to get elemental analysis and spectra.

The ir spectrum of the product showed the presence of OH (3400 cm^{-1}) and aldehyde groups (2802, 2755, and 1655 cm^{-1}). The aldehyde proton was readily confirmed by a peak at δ 9.70 in the ^1H nmr spectrum. Four doublets at δ 6.54, 6.67, 6.90, and 7.54 in ^1H nmr spectrum also indicated the presence of two thienyl rings, both having substituents at 2- and 5-positions. The chemical shift values could be compared with those of **1a** which showed δ 7.65 and 6.94 for 3-H and 4-H, respectively, and with that of 2,5-dimethylthiophene whose 3- and 4-H appeared at δ 6.58. One can readily relate δ 6.54 and 6.67 to the protons in the left thenyl ring and 6.90 and 7.54 to those in the right thienyl ring of **2a**. The peaks corresponding to CH_2 and CH at δ 3.28 and 5.03, respectively, showed an ABX pattern although the CH signal appeared as if it was a triplet. In addition, the ^{13}C nmr spectrum showed 12 peaks whose chemical shift values are consistent with the structure of an aldol adduct **2a**. Both mass spectral and elemental analyses supported the molecular formula of $C_{12}H_{12}O_2S_2$.

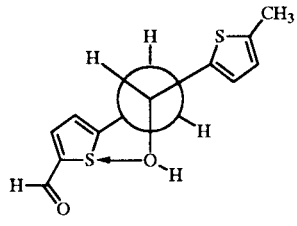
Compound **2a** could not be purified by vacuum distillation because it readily dehydrated during an attempt (at 0.01 mm Hg, and 180°), giving **5**. The dehydration product was a solid of mp 116-118° and its uv spectrum indicated the extended conjugation by a significant bathochromic shift (from 299 nm for **2a** to 385 nm for **5**). The trans relationship of the thenyl rings was established by the ^1H nmr coupling constant of 15.8 Hz in the -HC=CH- moiety. Furthermore, the trans wagging motion of hydrogens was observed at 945 cm^{-1} in the ir spectrum.



5

Although alcohols are converted to olefins by various means, dehydration by direct heating is rare. One similar example in the literature is the dehydration of 1-methylcyclopentanol in dimethyl sulfoxide at 160° to produce 1-methylcyclopentene [14]. The facile dehydration of **2a** may be related to the assistance of the S atom, which attracts the lone pair electrons of the O atom, and weakens the C-O bond. The most favorable conformation of **2a** seems to be such that S and O atoms are in close proximity, as shown in **I**.

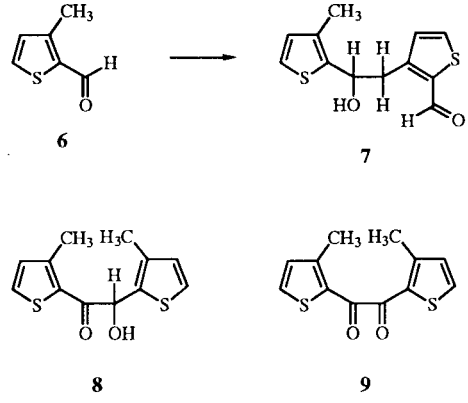
The aldol reaction also took place with 3-methylthiophene-2-carboxaldehyde (**6**) when it was subjected to similar reaction conditions as **1a**. Thus, **7** (3%) was isolated in addition to a thienoin, **8** (5%) and a thienil, **9** (3%)



I

(Scheme 3). The low yields of **7**, **8**, and **9** from **6** may be due to the steric hindrance of 3-methyl group. Thus, more than 70% of the starting material was recovered.

Scheme 3

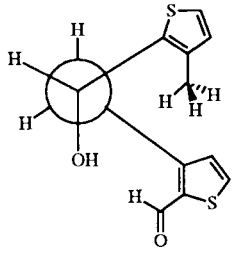


6 **7** **8** **9**

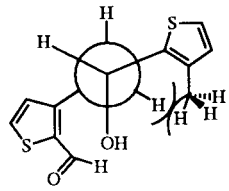
Compounds **7** and **2a** showed very similar patterns in their ir and nmr spectra. However, the CH_3 singlet shifted significantly upfield (δ 1.93) compared to **2a** (δ 2.40) or its starting material **6** (δ 2.59). This may be due to the spatial arrangement in **7**. The methyl protons may lie in the shielding region of the other thiophene ring (see below). The C=O stretching frequencies of **2a** and **7** are very similar (1655 and 1650 cm^{-1}, respectively) indicating that the carbonyl groups are far away from the hydroxyl group. If they were close, hydrogen bonding to the carbonyl oxygen atom would be expected, and this would shift the C=O stretching frequency. The chemical shift values for aldehyde protons were δ 9.70 for both compounds. Therefore, the effect of the carbonyl does not seem to be the cause of the upfield shift of the methyl protons of **7**.

In contrast to **2a**, compound **7** did not undergo dehydration upon heating to 180° for one hour. Apparently, the oxygen atom of the hydroxyl group is too far apart from the sulfur atom in **7**. Although an X-ray study could not be done for **7** because it was a gummy liquid, a molecular model study clearly showed that the CH_3 group could lie on the top of the other ring. An arrangement such as **III** would give trans olefin if dehydration reaction took place. But the S atom is located quite far from the O atom and

the effect which was thought to account for the dehydration of **2a** would be minimal, if any. On the other hand, the close proximity between the CH_3 and CH_2 protons would make the arrangement **III** less likely. The likely conformation for **7** is **II** in which the methyl group is on the top of the thienyl ring. Two thienyl rings are gauche and consequently, the dehydration product would be cis olefin. This is energetically unfavorable. In any event, the big difference between the chemical shifts of the methyl protons of **2a** and of **7** shows that they are conformationally quite different.



II



III

Intermolecular aldol reaction of **1a** did not take place in the presence of triethylamine, pyridine, borontrifluoride etherate, or titanium tetrachloride. When a strong base such as sodium hydroxide was used polymeric material was isolated which was not soluble in most organic solvents.

In contrast, 5-methylfurfural (**1b**) did not undergo the aldol reaction which might give **2b** in the presence of potassium cyanide. Only 5,5'-dimethylfuroin (**3b**) was isolated, in 20% yield, and no other organic component was detected in the reaction mixture. Depending on the catalysts the yields of **3b** could be improved, but unreacted starting material was recovered quantitatively in all cases. Apparently, the methyl proton is not acidic enough to form a carbanion in the presence of potassium cyanide. On the other hand, when **1b** and sodium hydroxide (0.2 equivalent) in ethanol and water were stirred at room temperature for 24 hours both aldol-type product **2b** (21%) and dehydration product **5b** (8%) were isolated in addition to the recovery of the starting material (60%).

Reaction of *p*-tolualdehyde with potassium cyanide also gave 4,4'-dimethylbenzoin (60%) and no aldol product was detected under various reaction conditions. When a stronger base such as sodium hydroxide was used no aldol reaction took place at room temperature, but the Canizzaro reaction took place resulting *p*-toluic acid and *p*-methylbenzyl alcohol.

EXPERIMENTAL

Melting points were determined on a MEL-TEMP apparatus and uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 1430 spectrophotometer and the ultraviolet-visible (uv) spectra were recorded on a Hitachi U-3200 double beam spectrophotometer. Nuclear magnetic resonance (nmr) spectra in deuteriochloroform were recorded on a Bruker 300 MHz FT-nmr spectrometer with tetramethylsilane as internal standard. Electron-impact mass spectra (ms) were obtained by Kratos MS 2S RFA spectrometer. Elemental analyses were performed by the M-H-W Laboratories, Phoenix, AZ.

Materials.

5-Methyl-2-thiophenecarboxaldehyde (**1a**), 5-methyl-2-furfural (**1b**), 3-methyl-2-thiophenecarboxaldehyde (**6**), and *p*-tolualdehyde were purchased from Aldrich Chemical Co. and distilled prior to use.

5-[2-Hydroxy-2-(5-methylthien-2-yl)ethyl]-2-thiophenecarboxaldehyde (**2a**).

A solution of **1a** (2.52 g, 20 mmoles) and potassium cyanide (0.13 g, 2 mmoles) in ethanol (30 ml) and water (10 ml) was heated at reflux for 24 hours. The solvents were removed under mild vacuum (bath temperature <50°) and the residue was partitioned in water (30 ml) and dichloromethane (30 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 30 ml). Combined organic layers were evaporated to dryness and the gummy residue was chromatographed on a column of silica gel (30 cm x 2 cm) prepared with benzene: (1) benzene, 400 ml; (2) 300 ml; (3) 300 ml; (4) benzene-chloroform, 9:1, 400 ml; (5) 300 ml; (6) 300 ml; (7) benzene-chloroform, 4:1, 300 ml; (8) 200 ml. Fraction 1 gave the unreacted **1a** (0.87 g, 35% recovery). Fraction 2 was mostly **1a** and trace of **4a** (0.10 g). Fraction 3 gave **4a** [13] (0.25 g, 10%). Fraction 4 was a mixture of **4a** and **3a** (trace). Fraction 5 gave **3a** [13] (0.50 g, 20%). Fraction 6 was a mixture of **3a** and **2a** (trace). Fractions 7 and 8 gave **2a** as a pale yellow viscous gel (0.76 g, 30%); ir (neat): 3400 (OH), 3062 (C=C-H), 2918 and 2855 (CH_3, CH_2), 2802 and 2755 (CH=O), 1655 (C=O) cm^{-1}; ^1H nmr: δ 2.41 (s, 3H, CH_3), 3.00 (s, 1H, OH), 3.28 (m, 2H, CH_2), 5.03 (t, 1H, CHOH, J = 6.4 Hz), 6.54 (d, 1H, thienyl-H, J = 3.4 Hz), 6.69 (d, 1H, thienyl-H, J = 3.4 Hz), 6.90 (d, 1H, thienyl-H, J = 3.8 Hz), 7.54 (d, 1H, thienyl-H, J = 3.8 Hz), 9.70 (s, 1H, CH=O); ^{13}C nmr: 15.2, 40.3, 70.3, 124.3, 124.6, 127.8, 136.6, 138.3, 142.4, 144.0, 151.5, 182.7 ppm; uv (methanol): 245 nm (ε 14000), 266 (13300), 299 (16400); ms: m/z 253 (21%, M^+ + H), 235 (55, M^+ - OH), 127 (93, CH_3-C_4H_2S-C^+HOH), 126 (85), 84 (100).

Anal. Calcd. for $C_{12}H_{12}O_2S_2$ (252.35): C, 57.11; H, 4.79; S, 25.41. Found: C, 57.04; H, 4.81; S, 25.19.

(*E*)-5-[2-(5-Methylthien-2-yl)ethen-1-yl]-2-thiophenecarboxaldehyde (**5a**).

Compound **2a** (0.50 g, 2 mmoles) was attempted to distill under vacuum (0.01 mm) by heating in an oil-bath (bath temperature 180°). No distillate could be collected. The hot liquid became a pale brown solid mass upon cooling. The solid was recrystallized from ethanol to give a pale yellow solid (0.30 g, 60%), mp 116-118°; ir (potassium bromide): 3080 (C=C-H), 2910 and 2850 (CH_3, CH_2), 2800 and 2730 (CH=O), 1665 (C=O), 947 (*trans* HC=CH) cm^{-1}; ^1H nmr: δ 2.46 (s, 3H, CH_3), 6.64 (d, 1H, thienyl-H, J = 3.5 Hz), an AB pattern centered at 6.53 and 7.15 (2H, *trans* HC=CH, J = 15.8 Hz), 6.90 (d, 1H, thienyl-H, J = 3.5 Hz), 7.03 (d, 1H, thienyl-H, J = 3.9 Hz), 7.59 (d, 1H, thienyl-H, J = 3.9 Hz), 9.80 (s, 1H, CH=O); ^{13}C nmr:

15.7, 118.9, 125.9, 126.2, 128.6, 137.2, 139.2, 139.4, 141.1, 141.5, 152.4, 182.3 ppm; uv (methanol): 272 nm (ε 10400), 289 (8900), 385 (12100); ms: m/z 234 (100%, M^+), 233 (19), 125 (50), 84 (58).

Anal. Calcd. for $C_{12}H_{10}OS_2$ (234.34): C, 61.50; H, 4.30; S, 27.37. Found: C, 61.70; H, 4.38; S, 27.49.

5-[2-Hydroxy-2-(5-methylfuran-2-yl)ethyl]-2-furfural (**2b**) and (*E*)-5-[2-(5-Methylfuran-2-yl)ethen-1-yl]-2-furfural (**5b**).

A solution of **1b** (1.17 g, 11 mmoles) was dissolved in ethanol (18 ml). Water (2 ml) and potassium hydroxide (0.17 g, 3 mmoles) were added and the mixture was stirred at room temperature for 24 hours. The ethanol was removed using a rotating evaporator under water-aspirator pressure (bath temperature <50°) and the residue was partitioned in water (30 ml) and dichloromethane (30 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 30 ml). Combined organic layers were evaporated to dryness and the resulting liquid was chromatographed on a column of silica gel (30 cm x 2 cm) prepared with benzene: (1) benzene, 950 ml; (2) benzene-chloroform, 9:1, 400 ml; (3) benzene-chloroform, 4:1, 300 ml; (4) benzene-chloroform, 2:1, 300 ml; (5) benzene-chloroform, 1:1, 1000 ml. Fraction 1 gave the unreacted **1b** (0.70 g, 60% recovery). Fraction 2 did not give any organic material. Fraction 3 gave **5b** (89 mg, 8%), mp 90-91°; ir (potassium bromide): 3060 (C=C-H), 2910 and 2840 (CH_3, CH_2), 2800 and 2747 CH=O), 1665 (C=O), 950 (*trans* HC=CH) cm^{-1}; ^1H nmr δ 2.35 (s, 3H, CH_3), 6.06 (d, 1H, furanyl-H, J = 3.2 Hz), 6.38 (d, 1H, furanyl-H, J = 3.3 Hz), 6.45 (d, 1H, furanyl-H, J = 3.8 Hz), an AB pattern centered at 6.75 and 7.09 (2H, *trans* HC=CH, J = 15.9 Hz), 7.24 (d, 1H, furanyl-H, J = 3.8 Hz), 9.55 (s, 1H, CH=O); uv (methanol): 386 nm (ε 21000), 278 (4200); ms: m/z 203 (15%, M^+ + 1), 202 (100, M^+), 145 (20), 131 (17), 115 (13).

Anal. Calcd. for $C_{12}H_{10}O3$ (202.21): C, 71.28; H, 4.98. Found: C, 71.43; H, 5.20.

Fraction 4 was a mixture of **5b** and **2b** (total 10 mg). Fraction 5 gave **2b** as a pale yellow viscous gel (0.24 g, 21%): ir (neat): 3410 (OH), 3110 (C=C-H), 2919 and 2875 (CH_3, CH_2), 2810 and 2750 (CH=O), 1660 (C=O) cm^{-1}; ^1H nmr δ 2.24 (s, 3H, CH_3), 3.27 (d, 2H, CH_2, J = 6.5 Hz), 5.06 (t, 1H, CHOH, J = 6.1 Hz), 5.93 (t, 1H, OH, J = 6.1 Hz), 6.14 (d, 1H, furanyl-H, J = 2.7 Hz), 6.34 (d, 1H, furanyl-H, J = 2.7 Hz), 7.11 (d, 1H, furanyl-H, J = 3.5 Hz), 7.19 (d, 1H, furanyl-H, J = 3.5 Hz), 9.53 (s, 1H, CH=O); uv (methanol): nm (ε) 287 (12100), 222 (6500); ms: m/z 203 (14%, M^+ - OH), 202 (100, M^+ - H_2O), 145 (22), 131 (19), 115 (14).

Anal. Calcd. for $C_{12}H_{12}O_4$ (220.22): C, 65.45; H, 5.49. Found: C, 65.25; H, 5.22.

3-[2-Hydroxy-2-(3-methylthien-2-yl)ethyl]-2-thiophenecarboxaldehyde (**7**), 3,3'-Dimethylthienoin (**8**), and 3,3'-Dimethylthienil (**9**).

A solution of potassium cyanide (0.27 g, 5 mmoles) in water (5 ml) was added to a solution of **6** (5.05 g, 40 mmoles) in ethanol (45 ml) gradually under nitrogen. The resulting deep blue solution was heated at reflux for 3 hours. Similar work-up to the reaction of **1a** and chromatography gave **6** (3.50 g, 70% recovery), **7** (0.15 g, 3%), **8** (0.25 g, 5%), and **9** (0.15 g, 3%). Compound **7** was a pale yellow gel; ir (neat): 3400 (OH), 3098 (C=C-H), 2922 and 2863 (CH_3, CH_2), 2750 (CH=O), 1650 (C=O) cm^{-1}; ^1H nmr δ 1.93 (s, 3H, CH_3), 2.43 (s, 1H, OH), 3.36 (m, 2H, CH_2), 5.15 (t, 1H, CHOH, J = 6.4 Hz), 6.66 (d, 1H, thienyl-H, J = 5.0 Hz), 6.89 (d, 1H, thienyl-H, J = 4.9 Hz), 7.07 (d, 1H, thienyl-H, J = 5.0 Hz), 7.53 (d, 1H, thienyl-H, J = 4.9 Hz), 9.70 (s, 1H, CH=O); uv (methanol): 278 nm (ε 12900), 240 (11500); ms: m/z 253 (15%, M^+ + H), 252 (35, M^+), 235 (44, M^+ - OH), 127 (100, CH_3-C_4H_2S-C^+HOH).

Anal. Calcd. for $C_{12}H_{12}O_2S_2$ (252.35): C, 57.11; H, 4.79; S, 25.41. Found: C, 56.86; H, 5.04; S, 25.06.

Compound **8** was a white solid, mp 79-83°; ir (potassium bromide): 3437 (OH), 3096 (C=C-H), 2919 (CH_3), 1653 (vs, C=O) cm^{-1}; ^1H nmr: δ 2.36 (s, 3H, 3'-CH_3), 2.59 (s, 3H, 3-CH_3), 4.47 (d, 1H, CHOH, J = 5.5 Hz), 5.80 (d, 1H, OH, J = 5.5 Hz), 6.80 (d, 1H, 4'-H, J = 5.1 Hz), 6.90 (d, 1H, 5'-H, J = 4.9 Hz), 7.18 (d, 1H, 4-H, J = 5.1 Hz), 7.39 (d, 1H, 5-H, J = 4.9 Hz), 9.70 (s, 1H, CH=O); uv (methanol): 278 nm (ε 14500); ms: m/z 253 (15%, M^+ + H), 252 (35, M^+), 235 (44, M^+ - OH), 127 (100, CH_3-C_4H_2S-C^+HOH).

Anal. Calcd. for $C_{12}H_{12}O_2S_2$ (252.35): C, 57.11; H, 4.79; S, 25.41. Found: C, 57.20; H, 4.87; S, 25.22.

Compound **9** was a white solid; mp 69-73°; ir (potassium bromide): 3105 (C=C-H), 2958 (CH_3), 1638 (C=O) cm^{-1}; ^1H nmr δ 2.55 (s, 6H, CH_3), 6.94 (d, 2H, 4-H, J = 4.9 Hz), 7.59 (d, 2H, 5-H, J = 4.9 Hz); uv (methanol): 307 nm (ε 25700), 248 (13000); ms: m/z 253 (15%, M^+ + H), 250 (100, M^+), 125 (97, CH_3-C_4H_2S-C^+=O).

Anal. Calcd. for $C_{12}H_{10}O_2S_2$ (252.35): C, 57.57; H, 4.03; S, 25.62. Found: C, 57.50; H, 3.88; S, 25.80.

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