

Full Paper

Synthesis of 5-Acetoxymethyl- and 5-Hydroxymethyl-2-vinylfuran

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Abstract: 5-Acetoxymethyl- and 5-hydroxymethyl-2-vinylfuran were synthesized by two routes. The first route starts from 2-methylfuran and the second from furfuryl acetate. The latter route, involving successive Vilsmeier-Haack and Wittig reactions, is suitable for producing 5-acetoxymethyl-2-vinylfuran and 5-hydroxymethyl-2-vinylfuran in 68% and 60% yields, respectively.

Keywords: Vilsmeier-Haack reaction, Wittig reaction, 5-acetylfurfuryl alcohol, 5-hydroxymethyl-2-vinylfuran.

Introduction

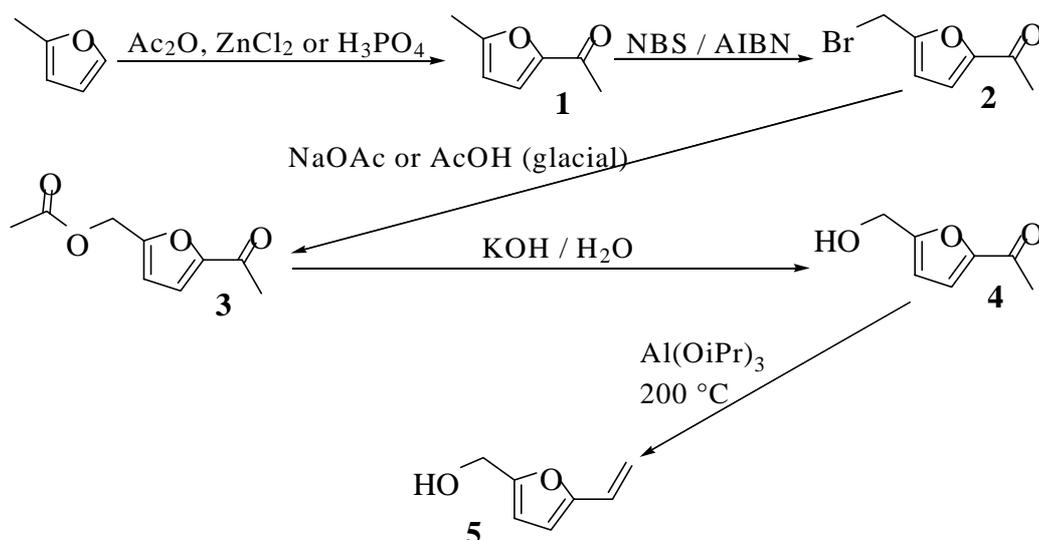
5-Hydroxymethyl-2-vinylfuran (**5**) was first synthesized in 70% overall yield by Dzhemilev *et al.* [1] by the reaction of 2-vinylfuran with 40% aqueous formaldehyde over a catalyst prepared by reducing Pd(acac)₂ (acac = acetylacetonate) with triethylaluminum in the presence of PPh₃. Compound **5** has also been prepared by low temperature hydroxyethylation of furfuryl alcohol with a large excess of acetaldehyde, using water as the solvent and a highly dealuminated H-mordenite as catalyst [2]. The mass spectrum of the acetate derivative of **5**, 5-acetoxymethyl-2-vinylfuran (**7**), has been reported [1],

but not its preparation, which should be achievable by simple acetylation of the alcohol group. In this work, two routes were explored to prepare **5**.

Results and Discussion

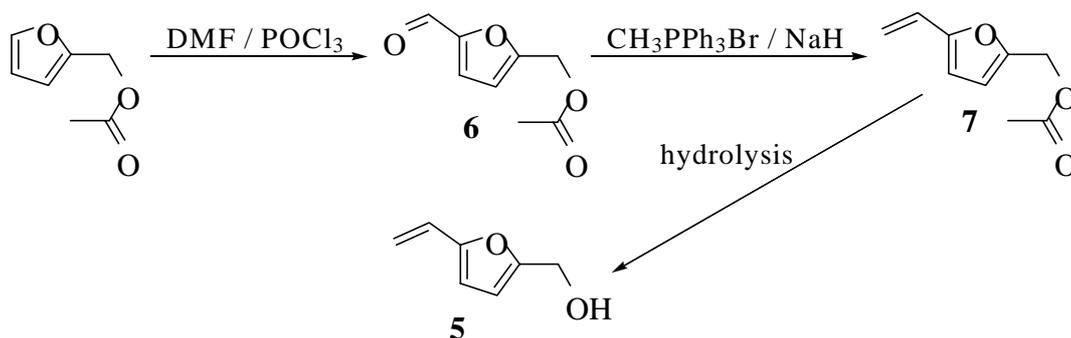
Schemes 1 and 2 present two routes to prepare **7** and **5**. The first route starts from 2-methylfuran and the second from furfuryl acetate. In the first route the starting material was acetylated with acetic anhydride under Friedel Crafts conditions using $ZnCl_2$ or H_3PO_4 as catalysts to obtain 5-methyl-2-acetylfuran (**1**, 60-70 %) [3]. The next step was bromination of **1** with *N*-bromosuccinimide (NBS) in CCl_4 using azobisisobutyronitrile (AIBN) as initiator. The use of AIBN favors the bromination of the methyl group [4] attached to the furan ring C5 position. 5-Bromomethyl-2-acetyl furan (**2**) is rather unstable and its purification was avoided, except to obtain a sample for spectroscopic characterization. The bromo derivative (**2**) is then reacted with glacial acetic acid to produce 5-acetyl-2-furfuryl acetate (**3**) [5], which is hydrolyzed with aqueous potassium hydroxide to give 5-acetyl furfuryl alcohol (**4**). The reduction of this compound under Meerwein-Ponndorf-Verley conditions followed by high temperature dehydration finally yields the target compound **5** [6], [7].

Scheme 1. First route to synthesize **5**.



The second route to **5** starting from furfuryl acetate was more efficient and rapid. First 5-formyl-furfuryl acetate (**6**) was synthesized *via* a Vilsmeier-Haack-reaction using *N,N*-dimethylformamide and phosphoryl chloride.

Scheme 2. Second route to synthesize **5**.



The use of similar reactions for the synthesis of 5-methyl-2-furfural [8] and 5-benzyloxymethyl-2-furfural [9, 10] were previously described in the literature. The aldehyde group of 5-formylfurfuryl acetate (**6**) was transformed into a vinyl group by a Wittig reaction with methyltriphenylphosphonium bromide and sodium hydride. 5-Hydroxymethyl-2-vinylfuran (**5**) was obtained after hydrolysis. The products were characterized by NMR, FTIR and mass spectroscopy data, which agreed with those reported in the literature [1, 2]. The MS peaks at 355.219 (**5**) and 439.224 (**7**) indicate that both furfuryl derivatives spontaneously undergo trimerisation with elimination of a hydroxy (**5**) and acetate group (**7**), respectively, under the experimental conditions of the ESI mass spectral analysis. Other side products derived from impurities were not detectable.

Conclusions

Compound **7** can be conveniently prepared from furfuryl acetate by a two step synthesis. The hydrolysis of **7** gives **5** in high yield. Although compound **5** can also be prepared starting from 2-methylfuran, the procedure is less efficient.

Experimental

General

1,2-Dichloroethane, dichloromethane, tetrachloromethane, and chloroform were used as solvents. They were freshly distilled under argon over CaH₂ before use. Diethyl ether was dried with sodium over benzophenone, distilled and stored under argon. *N,N*-Dimethylformamide (≥ 99 %, Merck), 2-methylfuran (≥ 99 %, Merck) and phosphoryl chloride (≥ 99 %, Merck) were distilled before using. Methyltriphenylphosphonium bromide (≥ 98 %, Merck), sodium hydride (95 %, Sigma-Aldrich) and furfuryl acetate (99 %, Sigma-Aldrich) were used as received. The ¹H- and ¹³C-NMR spectra in solution were measured at room temperature with a Varian Gemini 300 MHz spectrometer at 300 MHz (¹H-NMR) and 75.5 MHz (¹³C-NMR), respectively. Acetone-d₆ and CDCl₃ served as solvents and residual protons from CHCl₃ and acetone-d₆ and natural abundance ¹³C from ¹³CDCl₃ and acetone-d₆ were used as internal references. ATR-FTIR spectra were measured at room temperature at with a Golden Gate top part of Spectromat at a FTS-165 spectrometer of BioRad. The contact pressure was 5 bar and the ATR crystal was a sapphire. The intensity is indicated as follows: br. (broad), s. (strong), m. (medium) and w. (weak). Mass spectra were recorded using a Hewlett-Packard 5988a mass spectrometer.

5-Methyl-2-acetylfuran (**1**)

A mixture of acetic anhydride (1 mol) and 2-methylfuran (0.5 moles) was cooled to 0 °C in an Erlenmeyer flask and zinc chloride (0.015 moles) was added under stirring. After one hour at 0-5 °C the reacting mixture stayed at room temperature for three hours and was thoroughly washed with water, neutralized with sodium carbonate solution and dry with sodium sulfate. The solid was removed by filtration and the product was obtained by distillation under reduced pressure (78-82 °C at 14 mbar). When H₃PO₄ was employed, the addition of the catalyst (1.5 g, 85 %) to a mixture of 2

methylfuran (0.12 moles) and acetic anhydride (0.18 moles) was accomplished at 0°C. The reaction mixture was then maintained at 45°C for 2,5 hours and the procedure described above was followed to obtain the product. Yield 60-70%; ¹H-NMR (250 MHz, CDCl₃): δ 2.19 (s, CH₃), δ 2.22 (s, CH₃ acetyl group), δ 5,97 and δ 6.91 (d, H₃ and H₄ furan ring).

5-Acetyl-2-furfuryl acetate (3)

A mixture of compound **1** (1 equiv), 1 equiv of NBS and 10 % (wt. relative to NBS) of AIBN in CCl₄ was refluxed for one hour to produce 5-bromomethyl-2-acetylfuran (**2**). The reaction mixture was cooled to room temperature and succinimide crystals were filtered off. The solution was neutralized with Na₂CO₃ stirring for one hour, washed five times with water and dry with Na₂SO₄. Solvent was partially removed in a rotary evaporator until slightly brown-red oil was obtained. A solution of this crude product (11 g) and anhydrous sodium acetate (5 g) in glacial acetic acid (40 mL) was refluxed for 2 hours. The completion of the reaction was confirmed by TLC (n-hexane-ethyl acetate, 3:1) by the examination of samples each 20 minutes. The NaBr precipitate was removed by filtration and acetic acid was distilled at reduced pressure. The residue was washed several times with water and extracted with chloroform. The extract was dry Na₂SO₄, filtered out and chloroform was removed in a rotary evaporator. Yield 85 %; ¹H-NMR (250 MHz, CDCl₃): δ 2.08 (s, 3H acetate), δ 2.46 (s, 3H acetyl group), δ 5.08 (s, 2H CH₂ acetate), δ 6.52 and 7.12 (d, H₃ and H₄ furan ring)

5-Acetyl furfuryl alcohol (4)

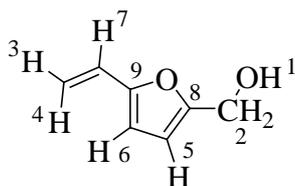
5-acetyl-2-furfuryl acetate (**3**) was refluxed for 1 h in a 20% KOH solution. The reaction mixture was cooled to room temperature and acidified gradually. At pH 7-8 phase separation started and at pH 5-6 the oil formed is extracted with ether, dry over sodium sulfate, filtered out and the solvent was finally removed. Yield 95 %; ¹H-NMR (250 MHz, CDCl₃): δ 2.35 (s, 3H acetyl group) and 4.57 (s, 2H CH₂OH), δ 6.35 and 7.07 (d, H₃ and H₄ furan ring)

5-Hydroxymethylvinylfuran (5)

From 5-acetyl furfuryl alcohol (4). A mixture of **4** (1 mol equiv.), aluminum isopropoxide (1 mol equiv.) and isopropanol (200 mL) in a round flask was heated to 50 °C under stirring. The temperature was steadily increased to 100 °C and the solvent and the acetone produced were simultaneously distilled off. When the mixture of the reaction became a light brown solid, the pressure was reduced to 3 mbar and the excess isopropanol was eliminated at 100 °C. The product was distilled at 200°C and 3 mbar. It was washed 3 times with water and extracted with chloroform. The solution was dried with anhydrous sodium sulfate and the solvent was finally removed. Yield 20 - 40 %, colorless liquid.

From 5-acetoxymethyl-2-vinylfuran (7). Compound **7** (11.13 mmol) and NaOH (1 M, 335 ml) were stirred for 10 h at 0 °C. The solution was extracted with diethylether (3 x 100 ml). The organic solution was dried with MgSO₄ and the solvent removed under reduced pressure. The crude yellow oil

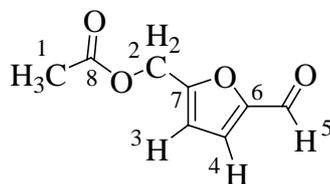
was purified by vacuum distillation to give the pure title compound ($p = 2 \times 10^{-1}$ mbar, $T = 40$ °C). Yield 89 %, colorless liquid.



$^1\text{H-NMR}$ (300 MHz, acetone- d_6): δ 4.27 (t, 1 H, $^3J_{\text{H}^1\text{H}^2} = 6.00$ Hz, H^1); 4.51 (d, 2 H, $^3J_{\text{H}^2\text{H}^1} = 6.00$ Hz, H^2); 5.11 (dd, 1 H, $^3J_{\text{H}^3\text{H}^7} = 11.30$ Hz, $^2J_{\text{H}^3\text{H}^4} = 1.50$ Hz, H^3); 5.58 (dd, 1 H, $^3J_{\text{H}^4\text{H}^7} = 17.50$ Hz, $^2J_{\text{H}^4\text{H}^3} = 1.50$ Hz, H^4); 6.27 (d, 1 H, $^3J_{\text{H}^5\text{H}^6} = 3.20$ Hz, H^5); 6.30 (d, 1 H, $^3J_{\text{H}^6\text{H}^5} = 3.20$ Hz, H^6); 6.53 (dd, 1 H, $^3J_{\text{H}^7\text{H}^4} = 17.50$ Hz, $^3J_{\text{H}^7\text{H}^3} = 11.30$ Hz, H^7); $^{13}\text{C-NMR}$ (75.5 MHz, acetone- d_6): δ 57.3 (s, C^2); 109.3 (s, $\text{C}^{3(4)}$); 109.9 (s, C^5); 111.7 (s, C^6); 126.1 (s, C^8); 153.3 (s, C^9); 156.3 (s, C^7); ATR-FTIR spectrum (ν , cm^{-1}): 3307 (br.), 3134 (w.), 3019 (w.), 2933 (w.), 2865 (w.), 1640 (w.), 1526 (m.), 1417 (w.), 1251 (m.), 1011 (s.), 980 (s.), 902 (s.), 791 (s.), 750 (m.), 631 (s.), 540 (s.), 491 (s.); MS (ESI): m/z calculated for $\text{C}_7\text{H}_8\text{O}_2$ [$\text{M}+1$] 125.137, found 355.219.

5-Formylfurfuryl acetate (**6**)

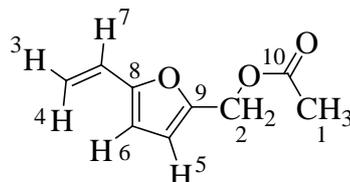
A mixture of *N,N*-dimethylformamide (414.17 mmol) and 1,2-dichloroethane (200 ml) was cooled to 0 °C and POCl_3 (310.63 mmol) was added over a period of 5 min. After stirring at 0 °C for 45 min, furfuryl acetate (107.04 mmol) was added over 5 min. The mixture was allowed to stand at room temperature for 24 h. The black solution was neutralized using 15 % aqueous Na_2CO_3 solution and extracted with diethylether (3 x 150 mL). The ether solution of the crude product was washed several times with distilled water and a saturated aqueous solution of NaCl. The solvent was removed on a rotary evaporator to afford a residue of ca. 100 mL total volume and NaHSO_3 aqueous solution (40 %, 100 mL) was added. After separation, white crystals of the bisulfite adduct are obtained. The bisulfite adduct was dissolved in a saturated NaHCO_3 solution (150 mL) and extracted with diethyl ether (3 x 100 mL). The organic phase was washed with water and dried with MgSO_4 . Diethyl ether was removed on a rotary evaporator to give a 52 % yield of pure **6** as a yellow liquid.



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.05 (s, 3 H, H^1); 5.07 (s, 2 H, H^2); 6.55 (d, 1 H, $^3J_{\text{H}^3\text{H}^4} = 3.56$ Hz, H^3); 7.17 (d, 1 H, $^3J_{\text{H}^3\text{H}^4} = 3.56$ Hz, H^4); 9.58 (s, 1 H, H^5); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 20.2 (s, C^1); 57.3 (s, C^2); 112.2 (s, C^3); 121.7 (s, C^4); 152.4 (s, C^6); 155.1 (s, C^7); 169.8 (s, C^8); 177.4 (s, C^5); ATR-FTIR spectrum (ν , cm^{-1}): 3124 (w.), 2950 (w.), 2835 (w.), 1746 (s.), 1681 (s.), 1589 (w.), 1526 (s.), 1438 (m.), 1403 (m.), 1377 (m.), 1274 (m.), 1232 (s.), 1026 (s.), 988 (m.), 945 (m.), 812 (m.), 779 (m.), 757 (m.), 724 (w.), 603 (w.); MS (ESI): m/z calculated for $\text{C}_8\text{H}_8\text{O}_4$ [$\text{M}+1$] 169.147, found 169.045.

5-Acetoxymethyl-2-vinylfuran (7)

Methyltriphenylphosphonium bromide (34.44 mmol) and diethyl ether (150 mL) were cooled under an argon atmosphere at 0 °C. The slurry was stirred and NaH (68.87 mmol) was added. After continuously stirring at 0 °C for 1 h, 5-formylfurfuryl acetate (6, 22.96 mmol) dissolved in diethyl ether (20 mL) was slowly added. The black mixture was neutralized with Na₂CO₃ (15 %) after stirring 24 h. The aqueous solution was extracted with diethyl ether (3 x 100 mL). An orange oil was obtained from the organic phase, which was purified by vacuum distillation (P = 2 x 10⁻¹ mbar, T = 50 °C). Yield 68 %, colorless liquid.



¹H-NMR (300 MHz, CDCl₃): δ 2.04 (s, 3 H, H¹); 5.01 (s, 2 H, H²); 5.15 (dd, 1 H, ³J_{H³H⁷} = 11.29, ²J_{H³H⁴} = 1.23, H³); 5.66 (dd, 1 H, ³J_{H⁴H⁷} = 17.55, ²J_{H³H⁴} = 1.23, H⁴); 6.19 (d, 1 H, ³J_{H⁵H⁶} = 3.26, H⁵); 6.35 (d, 1 H, ³J_{H⁵H⁶} = 3.26, H⁶); 6.44 (dd, 1 H, ³J_{H⁴H⁷} = 17.55, ³J_{H³H⁷} = 11.29, H⁷); ¹³C-NMR (75.5 MHz, CDCl₃): δ 20.8 (s, C¹); 58.1 (s, C²); 108.7 (s, C⁶); 112.3 (s, C³⁽⁴⁾); 113.1 (s, C⁵); 124.7 (s, C⁷); 148.8 (s, C⁸); 153.7 (s, C⁹); 170.6 (s, C¹⁰); ATR-FTIR spectrum (ν, cm⁻¹): 3124 (w.), 3103 (w.), 2978 (w.), 2942 (w.) 1740 (s.), 1642 (w.), 1526 (w.), 1444 (w.), 1373 (m.), 1358 (m.), 1252 (m.), 1228 (s.), 1191 (m.), 1018 (s.), 980 (m.), 956 (m.), 937 (m.), 905 (m.), 791 (s.), 748 (m.), 701 (m.), 639 (w.), 612 (w.), 600 (w), 571 (w.); MS (ESI): m/z calculated for C₉H₁₀O₃ [M+1] 167.174, found 439.224.

Acknowledgements

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