Condensation Reactions of a Comenaldehyde Derivative

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Condensation reactions of comenaldehyde methyl ether (I) with malonic acid, ethyl cyanoacetate, and cyanoacetamide to give β -(5-methoxy-4H-pyran-4-on-2-yl)acrylic acid (II), ethyl 2-cyano-3-(5-methoxy-4H-pyran-4-on-2-yl)propenamide (IV), respectively, are described. Ultraviolet absorption spectra for 2-hydroxymethyl-5-methoxy-4H-pyran-4-one, I and II are presented.

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The synthesis of comenaldehyde methyl ether (I) has been reported from this (1) and other laboratories (2). In the present note we report condensation reactions of I with malonic acid, cyanoacetic ester, and cyanoacetamide.

Reaction of I with malonic acid in pyridine under Knoevenagel conditions required five to six days to give a 14% yield of β -(5-methoxy-4H-pyran-4-on-2-yl)acrylic acid (II). The reaction mixture was heated at the beginning of the reaction, but attempts to increase the yield through longer heating led to extensive decomposition. When malonic acid was reacted with I in dry pyridine in the presence of a weakly basic ion exchange resin (Amberlite IR-4B), the yield of II increased to 34%. Ir and uv spectral and analytical data (Experimental) support the structure assigned. Comparison of the uv spectra of I and 2-hydroxymethyl-5-methoxy-4H-pyran-4-one indicates a remarkable similarity. Possibly the carbonyl group of I is strongly solvated, or forms a hemiacetal in methanol solution. The uv spectrum of II shows the expected (4) bathochromic shift relative to the 267 nm band in the spectrum of I, with an increase of approximately 75% in intensity.

Additional condensation reactions were studied with I. In our hands, the best conditions for reaction of I with cyanoacetic ester involved use of a catalytic amount of glycine in ethanol containing a small quantity of acetic acid. The exact role of the glycine is incompletely understood. A 69% yield of crude ethyl 2-cyano-3-(5-methoxy-4H-pyran-4-on-2-yl)propenoate (III) was obtained. The glycine procedure also was applicable to condensation of I

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with cyanoacetamide; in this case a 43% yield of 2-cyano-3-(5-methoxy-4H-pyran-4-on-2-yl)propenamide (IV) was obtained. Since IV was insoluble in all solvents studied, it was purified by lixiviation with a series of organic solvents and with water.

EXPERIMENTAL

Melting points are uncorrected. Infrared absorption spectra were determined with a Perkin-Elmer Model 21 spectrometer. Ultraviolet absorption spectra of 1.00×10^{-4} M absolute methanol solutions were determined with a Cary Model 11-MS recording spectrophotometer, and are reported as λ max in nm (log ϵ). Analyses are by A. Bernhardt Laboratories, Elbach über Engels Kirchen, Germany.

2 - Hydroxymethyl - 5 - methoxy - 4H - pyran - 4 - one.

This substance was prepared from kojic acid by a literature procedure (5); uv: 217 (4.20) and 266 (4.07).

Comenaldehyde Methyl Ether (I).

This substance was prepared by manganese dioxide (1) or selenium dioxide (2b) oxidation of 2-hydroxymethyl-5-methoxy-4H-pyran-4-one; uv: 217 (4.25) and 267 (4.08).

β-(5-Methoxy-4H-pyran-4-on-2-yl)acrylic Acid (II).

The procedure described is a modification of that of Allen and Van Allan (6). Two grams of comenaldehyde methyl ether and 1.5 g. of dried malonic acid in 30 ml. of dry pryidine were heated under reflux on a steam bath for 2.5 hours. By the end of the heating period, the aldehyde and malonic acid had dissolved. The solution was permitted to stand five days at room temperature and then was returned to the steam bath for 1 hour. Then the contents of the flask were cooled, poured over ice, and the resulting mixture allowed to stand overnight in a refrigerator. The resulting fine crystals were collected by filtration and dried, yield 0.35 g. (14%). The filtrate was then extracted with chloroform. Solvent was removed from both chloroform extract and aqueous layer. However, no additional acrylic acid derivative was isolable. Recrystallization of the crystalline product was effected from the minimal quantity of absolute ethanol to give white crystals, m.p. 243-245°; ir (potassium bromide): 3400, 3090, 2940, 1727 (carboxyl CO), 1658 (pyrone CO), 1620, 1594, 1562, 1468, 1420, 1295, 1250, 1185, 1170, 1015, 980, 965, 945, and 875 cm⁻¹; uv: 233 (4.27) and 277 (4.31).

Anal. Calcd. for C₉H₈O₅: C, 55.10; H, 4.11. Found: C, 55.05, 55.02; H, 4.33, 4.38.

Synthesis of the title compound also was effected as follows. A 1.0-g. quantity of comenaldehyde methyl ether and 0.7 g. of malonic acid were added to 50 ml. dry pyridine. An approximately 1.5-g. quantity of the ion exchange resin Amberlite IR-4B (Mallinckrodt) was added to the reaction mixture which was stirred (magnetic stirring bar) in a glass-stoppered flask at room temperature for 48 hours. The resin was removed by filtra-

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tion and solvent removed from the filtrate by flash evaporation with a minimum of heating. The product light brown powder was washed with cold water and collected; yield 0.44 g. (34%). Recrystallization from the minimal amount of absolute ethanol gave the product acid, m.p. 243-245°.

Ethyl 2-Cyano-3-(5-methoxy-4H-pyran-4-on-2-yl)propenoate (III).

Glycine (30 mg.) was added to 0.5 ml. of glacial acetic acid in 50 ml. absolute ethanol. To this solution was added, all at once, 1.6 g. of ethyl cyanoacetate and 1.0 g of comenaldehyde methyl ether. The reaction mixture was heated under reflux for two hours, and then was stirred (magnetic bar) at room temperature for eight hours. The yellow powder which precipitated was collected by filtration, washed with ice water and air-dried, yield 1.1 g. (69%). The analytically pure compound, m.p. 217-219°, was obtained as a light yellow powder by recrystallization from absolute ethanol.

Anal. Calcd. for C₁₂H₁₁NO₅: C, 57.83; H, 4.45; N, 5.62. Found: C 57.83; H, 4.55; N, 5.77.

2-Cyano-3-(5-methoxy-4H-pyran-4-on-2-yl)propenamide (IV).

Glycine (30 mg.) was added to a suspension of 0.55 g. of cyanoacetamide in 50 ml. of absolute ethanol containing 0.5 ml. of glacial acetic acid. The resulting suspension was heated to effect solution, and then to the warm solution was added, all at once, 1.0 g. of comenaldehyde methyl ether. The reaction mixture was heated under reflux for two hours; the aldehyde dissolved initially, and then there occurred slow formation of a yellow precipitate. The mixture was stirred (magnetic bar) at room

temperature for an additional eight hours. The yellow pecipitate was collected by filtration, washed with a small amount of water, and air-dried, yield 0.62 g. (43%). The substance was insoluble in the common solvents, and was purified by successive lixiviations with the following hot solvents: ethanol, carbon tetrachloride, methylene chloride and water, to give the analytically pure title compound, m.p. 259-261° dec. Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.64; N, 12.73. Found: C, 54.44; H, 3.69; N, 12.56.

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