The Synthesis of 5- and 6-Acyl-2(1*H*)-pyrimidinones

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The synthesis of 5-acyl-2(1*H*)-pyrimidinones is described. In addition, one example of the hitherto unknown 6-acyl-2(1*H*)-pyrimidinones has been prepared.

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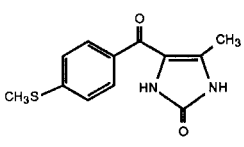
A number of 4-acylimidazolones have been prepared and evaluated for positive inotropic activity in our laboratories [1]. One of these compounds, enoximone **1**, is currently in advanced clinical trials. In order to investigate the effects of ring size on the positive inotropic activity, 5- and 6-acyl-2(1*H*)-pyrimidinones were prepared [2]. Interestingly, only one example of structures of this type, *i.e.* **2c**, has been previously reported [3].



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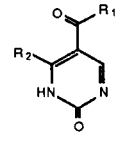
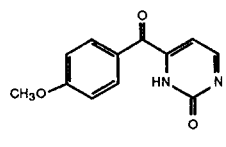


2a, R_1 = C_6H_5, R_2 = CH_3
2b, R_1 = R_2 CH_3
2c, R_1 = C_6H_5, R_2 = CO_2CH_3



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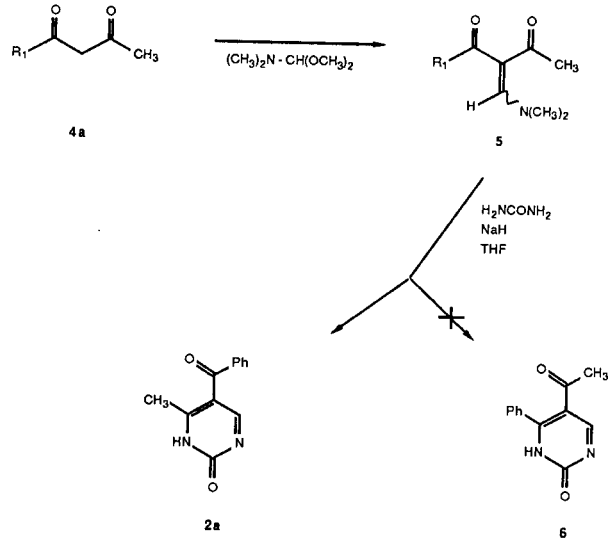
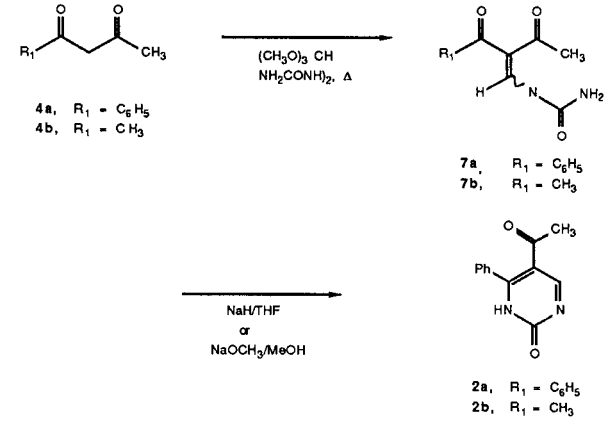
In this paper we describe the synthesis and characterization of 5- and 6-acyl-2(1*H*)-pyrimidinones **2a**, **2b**, and **3**, respectively. The synthesis of **2a** was accomplished by condensing benzoylacetone **4a** and dimethylformamide dimethyl acetal yielding the vinylogous amide **5** in good yield [4]. Cyclization of **5** with urea using sodium hydride in dry tetrahydrofuran gave **2a** in a modest 30% yield. Theoretically, the cyclization reaction could give two isomeric pyrimidinones, *i.e.* **2a** and **6**. In practice, however, the alternate cyclization to give **6** was not observed.

The structure of **2a** was established on the basis of long-range carbon-proton coupling using single frequency decoupling ^{13}C nmr techniques. The broad multiplet for the benzoyl carbonyl observed at 190.3 ppm collapsed to a singlet upon irradiation of the aromatic protons. A similar decoupling of the methyl protons resulted in no change in the multiplicity of the benzoyl carbonyl signal.

An alternate synthesis of **2a** was carried out by utilizing a modification of the method reported by Miyashita *et al.* [5] for the synthesis of uracil derivatives. Thus, condensation of **4a** with urea and either trimethyl orthoformate or triethyl orthoformate gave **7a** as a mixture of diastereoisomers in 56% yield. Subsequent cyclization of **7a** with urea in the presence of sodium hydride gave **2a** in



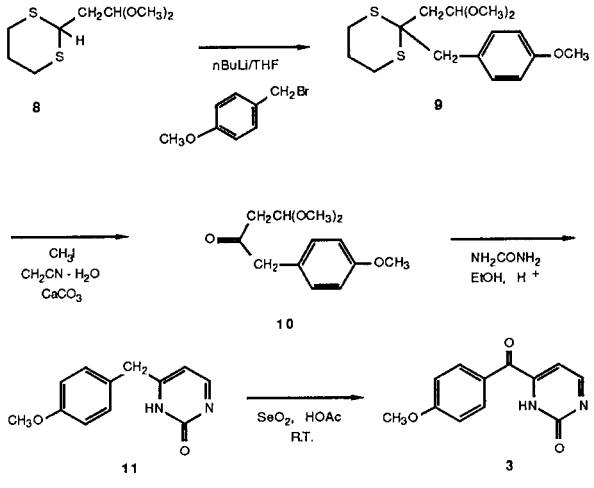
moderate yield. Once again, the alternative cyclization to give **6** was not observed. In a similar fashion **2b** was prepared from **4b** *via* the intermediate **7b** in modest yield.



The synthesis of the 6-benzoyl-2-pyrimidinone **3** was carried out starting with the dithiane **8** [6]. Condensation of the lithium anion of **8** with freshly prepared *p*-methoxybenzyl bromide [7] gave **9** in 85% yield. Compound **9** was hydrolyzed to the ketone **10** in 68% yield using methyl iodide in buffered aqueous acetonitrile [8]. Cyclization of

ketone **10** with urea using 2 equivalents of hydrochloric acid gave pyrimidinone **11** in 65% yield. Finally, selenium dioxide oxidation of **11** gave the desired 2-pyrimidinone **3** in 35% yield.

In conclusion, the condensation of vinylogous imides with urea provides a convenient synthesis of 5-acyl-2(1*H*)-pyrimidinones. In addition, the synthesis of the first example of a 6-acyl-2(1*H*)-pyrimidinone has been achieved by condensation of the appropriate β-ketoacetal with urea followed by selenium dioxide oxidation.



EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. High performance liquid chromatography (hplc) purifications were achieved on a Waters prep 500 liquid chromatograph. The infrared and ultraviolet spectra were obtained using Perkin Elmer 180 spectrometers. The nuclear magnetic resonance spectra were recorded on Varian FT80A and VXR300 spectrometers. The chemical shifts are given in parts per million from tetramethylsilane as the internal reference standard. Long range carbon-proton coupling was established in the ^{13}C nmr spectrum of **2a** using single frequency decoupling techniques. Mass spectra were obtained on a Finnegan MAT4600 mass spectrometer.

3-[(Dimethyl)aminomethylene]-1-phenyl-2,4-butanedione (**5**).

Benzoylacetone **4a** (24.00 g, 0.15 mole) and *N,N*-dimethylformamide dimethylacetal (18.84 g, 0.158 mole) were stirred overnight at room temperature under argon. The mixture was heterogeneous initially but slowly became a homogeneous solution. The resulting orange liquid was concentrated *in vacuo* then dissolved in tetrahydrofuran. The tetrahydrofuran solution was heated then slowly diluted with hexane until turbid. An orange gum precipitated which solidified on cooling giving 25.20 g (78%) of **5**, mp 72-74°; ^1H nmr (deuteriochloroform): δ 7.80 (m, 3H, aromatic, vinyl), 7.40 (m, 3H, aromatic), 2.85 (s, 6H, $2CH_3$), 2.00 (s, 3H, CH_3); ir (5% deuteriochloroform): ν 1650 cm^{-1} (C=O); uv (ethanol): λ max = 293 nm, ε = 15,300.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.57; H, 6.98; N, 6.22.

5-Benzoyl-6-methyl-2-(1*H*)-pyrimidinone (**2a**).

a. Urea (1.90 g, 0.032 mole) and sodium hydride (60% in mineral oil) (1.57 g, 0.039 mole) were warmed to 55° in dry tetrahydrofuran under an argon blanket. After 15 minutes at 55°, **5** (6.52 g, 0.030 mole) was added portionwise over 15 minutes. The reaction mixture turned a yellow color and a basic gas was evolved. The reaction mixture was stirred and heated at 55° overnight under argon, cooled to room temperature and neutralized with acetic acid (4.00 ml). The solvent was removed *in vacuo* and the resulting residue was partitioned between dichloromethane (100 ml) and water (100 ml). A solid was present in the aqueous layer. The solid was collected by filtration and air dried giving 1.95 g (30%), mp 232-235°. Recrystallization gave the analytical sample of **2a**, mp 238-240°; ^1H nmr (dimethylsulfoxide-d_6): δ 8.20 (s, 1H, pyrimidinone-H), 7.85 (m, 5H, aromatic), 2.35 (s, 3H, CH_3); ^{13}C nmr broad band decoupled (deuteriochloroform/trifluoroacetic acid): 190.3 (s, benzoyl carbonyl, line width at half height 2.0 Hz), 190.4 (m, benzoyl carbonyl, line width at half height 11.2 Hz); ^{13}C nmr single frequency decoupled aromatic protons 7.8 ppm: 190.4 (s, benzoyl carbonyl, line width at half height 2.4 Hz); ^{13}C nmr single frequency decoupled methyl protons 2.9 ppm: 190.4 (m, benzoyl carbonyl line width at half height 10.5 Hz); ms: (m/e) 214 (M^+); uv (ethanol): λ max = 265 nm, ε = 17,400; ir (potassium bromide): ν 1740 (C=O).

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.07; H, 4.79; N, 13.08.

b. *N*-(2-Benzoyl-3-oxo-1-butenyl)urea **7a** (4.65 g, 0.020 mole) was added to a stirred suspension of sodium hydride (60% in mineral oil) (1.20 g, 0.030 mole) in dry tetrahydrofuran at room temperature. The resulting mixture was then stirred and heated overnight at 50-60°. The brown mixture was allowed to cool to room temperature then neutralized with acetic acid. The mixture was concentrated *in vacuo* and the residue was extracted with a two phase dichloromethane/water mixture. Filtration of the mixture gave 1.00 g (23%), mp 235-236°. Recrystallization from ethanol gave colorless needles of **2a**, mp 238-240°.

N-(2-Benzoyl-3-oxo-1-butenyl)urea (**7a**).

Benzoylacetone **4a** (12.98 g, 0.080 mole) was added to a stirred mixture of powdered urea (6.01 g, 0.10 mole) and triethyl orthoformate (13.34 g, 0.090 mole) under an argon atmosphere. The resulting suspension was rapidly warmed to 145° where it liquified and began to reflux. The reaction mixture was then heated and stirred in an open flask for approximately 10 minutes at 145°. After it solidified the mixture was allowed to cool to room temperature then transferred to a Buchner funnel and the solid was crushed with a stirring rod. The solid was washed with water (100 ml) and dichloromethane (100 ml) then air dried giving 10.48 g (56%) of a yellow powder, mp 185-187°.

Recrystallization from 50% ethanol-water gave **7a** as yellow needles, mp 185-187°; ir (potassium bromide): ν 1760, 1720 cm^{-1} (C=O); uv (ethanol): λ max = 294 nm, ε = 19,700; ^1H nmr (dimethylsulfoxide-d_6/-deuterium oxide): δ 7.82 (s, 1H), 7.65-7.40 (m, 6H), 2.25 (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.24; N, 12.07. Found: C, 61.91; H, 5.24; N, 12.02.

N-(2-Acetyl-3-oxo-1-butenyl)urea (**7b**).

2,4-Pentanedione **4b** (5.14 g, 0.050 mole), powdered urea (3.20 g, 0.050 mole) and trimethyl orthoformate (7.42 g, 0.050 mole) were heated (140°) and stirred until the mixture solidified. The crude solid was transformed to a Buchner funnel and washed with dichloromethane and water then air dried giving 3.62 g (45%) as a yellow solid.

Recrystallization from ethanol-water gave 1.62 g (19%) of **7b**, mp 191-192°; ^1H nmr (dimethylsulfoxide-d_6): δ 9.50 (d, J = 6.0 Hz, 1H, NH), 8.75, 8.30 (s, 1H, isomeric vinyl H), 7.35 (2H, NH_2), 2.20 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); uv (ethanol) λ max = 291 nm, ε = 20,200; ir (potassium bromide): ν 1730, 1700, 1660, and 1640 cm^{-1}.

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.38; H, 5.90; N, 16.31.

5-Acetyl-6-methyl-2(1*H*)-pyrimidinone (**2b**).

Compound **7b** (11.20 g, 0.0699 mole) was added to a solution of sodium (1.84 g, 0.080 mole) in dry methanol (175 ml). The resulting yellow solution was stirred and heated at reflux for 1.5 hours then allowed to cooled to room temperature and neutralized with acetic acid (5.00

ml). Filtration of the precipitated material afforded the crude product (6.00 g) as a light tan solid.

Recrystallization from methanol gave 3.65 g (35%), mp 198-200°. A further recrystallization afforded pure **2b**, mp 204-205°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.75 (s, 1H, pyrimidinone-4H), 2.50 (s, 3H, CH_3), 2.38 (s, 3H, CH_3); uv (ethanol): λ max = 257 nm, ε 18,750.

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.22. Found: C, 54.86; H, 5.39; N, 18.22.

2-(2,2-Dimethoxyethyl)-1,3-dithiane (**8**).

Acetic acid (373 ml, 6.52 moles) and boron trifluoride etherate (186.5 ml, 1.52 moles) were added to chloroform (2 l) with stirring under a nitrogen atmosphere. To this stirred mixture was added a mixture of malonaldehyde bis(dimethyl acetal) (1 kg, 6.09 moles) and 1,3-propanedithiol (165 g, 1.52 moles) in chloroform (3 l) over a 2 hour period at room temperature. The mixture was stirred overnight then heated to reflux for 10 minutes. The reaction mixture was cooled to room temperature then extracted three times with 1 l of water and twice with 500 ml of 10% potassium hydroxide. The chloroform solution was dried over anhydrous magnesium sulfate and filtered through anhydrous sodium sulfate. The filtrate was concentrated to a reddish brown liquid on the rotary evaporator then distilled (Kugelrohr) at 90-120°, 0.03 mm, using two collection bulbs [9]. The second bulb contained the product 218 g (69%). A portion (50 g) of this crude product was purified by hplc (15% ethyl acetate-85% hexane) giving 33.0 g of **8** [10]; ^{1}H nmr (deuteriochloroform): δ 4.65 (t, J = 8.0 Hz, 1H, CH), 4.33 (t, J = 8.0 Hz, 1H, CH), 3.33 (s, 6H, $2CH_3$), 3.00-2.66 (m, 4H, $2CH_2$), 2.20-1.80 (m, 4H, $2CH_2$).

Anal. Calcd. for $C_8H_6O_2S_2$: C, 46.12; H, 7.74; S, 30.78. Found: C, 45.92; H, 7.50.

2-(2,2-Dimethoxyethyl)-2-[(4-methoxyphenyl)methyl]-1,3-dithiane (**9**).

n-Butyllithium (48 ml of a 1.5 *M* solution, 0.072 mole) was added to a stirred solution of **8** (13.38 g, 0.066 mole) in dry tetrahydrofuran (300 ml) at -50°. The solution was allowed to warm to -30° for 1 hour then cooled below -50° and freshly prepared 4-methoxybenzyl bromide (13.27 g, 0.066 mole) [11] was added dropwise. The reaction mixture was maintained at -50° for an hour then stored at -20° overnight. It was allowed to warm to 0° then quenched with a saturated solution of ammonium chloride. The tetrahydrofuran layer was separated, washed with brine, and dried over magnesium sulfate. Filtration through celite followed by concentration of the filtrate *in vacuo* gave an oil. The oil was eluted with 15% ethyl acetate-85% hexane on hplc giving 18.50 g (85%) of **3**; ^{1}H nmr (deuteriochloroform): δ 7.25 (d, J = 8.0 Hz, 2H, aromatic), 6.80 (d, J = 8.0 Hz, 2H, aromatic), 4.70 (s, 1H, CH), 3.75 (s, 3H, OCH_3), 3.30 (s, 6H, $2OCH_3$), 3.20 (s, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 2.25-1.35 (m, 4H, $2CH_2$).

Anal. Calcd. for $C_{16}H_{24}O_3S_2$: C, 58.50; H, 7.36; S, 19.52. Found: C, 58.83; H, 7.48; S, 19.27.

4,4-Dimethoxy-1-(4-methoxyphenyl)-4-methyl-2-butanone (**10**).

Iodomethane (21.00 g, 0.14 mole) was added to a stirred mixture of **19** (8.10 g, 0.024 mole) and calcium carbonate (9.86 g, 0.0986 mole) in 80% acetonitrile-water at room temperature. The mixture was stirred for 24 hours then calcium carbonate (9.86 g) and iodomethane (21.00 g) were added and stirring was continued for an additional 24 hours. The reaction mixture was poured into an ether-water mixture and the ether layer was separated and extracted twice with water then with 10% potassium carbonate. The ether layer was separated and dried over potassium carbonate then filtered and concentrated *in vacuo* giving 4.37 g (75%) of a yellow liquid. Flash chromatography (silica), eluting with 25% ethyl acetate-75% hexane, gave 4.00 g (68%) of **10** as a pale yellow oil; ^{1}H nmr (deuteriochloroform): δ 7.07 (m, 2H, aromatic), 6.80 (m, 2H, aromatic), 4.75 (t, J = 8.0 Hz, 1H, CH), 3.75 (s, 3H, OCH_3), 3.63 (s, 2H, CH_2), 3.30 (s, 6H, $2OCH_3$), 2.70 (d, J = 8.0 Hz, 2H, CH_2); ir (10% chloroform): ν 1715 cm^{-1} (C=O); uv (ethanol): λ max = 226 nm, ε = 8,360.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.20; H, 7.75.

6-[(4-Methoxyphenyl)methyl]-2(1*H*)-pyrimidinone (**11**).

Urea (0.600 g, 0.01 mole) and **10** (2.05 g, 0.0086 mole) were heated to reflux in absolute ethanol (13.00 ml). Concentrated hydrochloric acid (1.65 ml, 0.0196 mole) was added dropwise over 15 minutes then heating was discontinued. The resulting reaction mixture was stirred overnight at room temperature. A copious tan solid precipitated. The solid was removed by filtration then suspended in water (100 ml). The *p*H was adjusted to 4.0 with 10% potassium hydroxide. The suspended solid was collected by filtration, washed with water and air dried giving 1.20 g (65%) of crude **11**, mp 208-211° dec. Recrystallization from ethanol (75 ml) gave 0.8 g of **11**, mp 208-210°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.85 (d, J = 6.0 Hz, pyrimidinone-H), 7.15 (d, J = 7.0 Hz, 2H, benzene), 6.8 (d, J = 7.0 Hz, 2H, benzene), 6.15 (d, J = 6.0 Hz, 1H, pyrimidinone-H), 3.75-3.60 (m, 5H, CH_2, OCH_3); ir (KBr): 1650 cm^{-1} (C=O); uv (ethanol): λ max = 303 nm, ε = 5,980.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60; N, 12.96. Found: C, 66.63; H, 5.64; N, 12.57.

6-(4-Methoxybenzoyl)-2(1*H*)-pyrimidinone (**3**).

Selenium dioxide (1.86 g, 0.0167 mole) and **11** (3.46 g, 0.0167 mole) were stirred in glacial acetic acid under an argon atmosphere overnight at room temperature. The resulting reddish colored mixture was filtered through celite and concentrated on the rotary evaporator. The resulting residue was dissolved in a methanol-water solution and treated with charcoal. Filtration through celite followed by concentration of the filtrate afforded crude **3** as a cream colored solid (1.20 g, 35%). Several recrystallizations from methanol-water gave the analytical sample of **3**, mp 239-241°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.12 (d, J = 6.0 Hz, 1H, pyrimidinone-H), 7.90 (m, 2H, benzene), 7.05 (m, 2H, benzene), 6.60 (d, J = 6.0 Hz, 1H, pyrimidinone-H), 4.83 (s, 3H, OCH_3); ir (potassium bromide): ν 1660 (C=O), 1645 cm^{-1} (NHCONH); uv (ethanol): λ max = 306 nm, ε = 12,400.

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.20; H, 4.27; N, 12.29.

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[9] A simple Kugelrohr distillation using two bulbs easily separates the dithiane dimethyl acetal from malonaldehyde dimethyl acetal. We are describing the synthesis and this modification, along with the spectral characteristics, since the spectra have not been previously published.

[10] The compound is relatively stable at this point and we have stored it at room temperature for up to 2 years with very little decomposition.

[11] The *p*-methoxybenzyl bromide was prepared from *p*-methoxybenzyl alcohol and phosphorous tribromide followed by Kugelrohr distillation. It was used within two days of its preparation. *p*-Methoxybenzyl chloride may be substituted with very little change in yield.