Improved Syntheses of 4(3*H*)-Pyrimidinones

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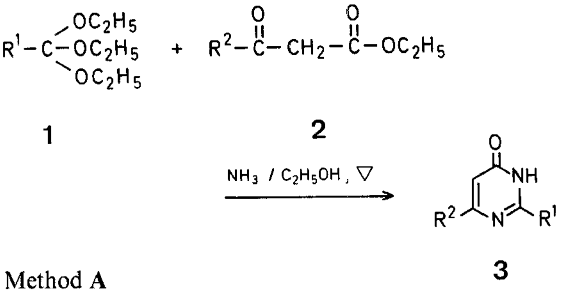
Methods presently used for synthesis of 4(3*H*)-pyrimidinones generally involve long reaction times and/or troublesome workup procedures[1]. We describe herein more convenient procedures for synthesis of 4(3*H*)-pyrimidinone and some 2-substituted and 2,6-disubstituted derivatives.

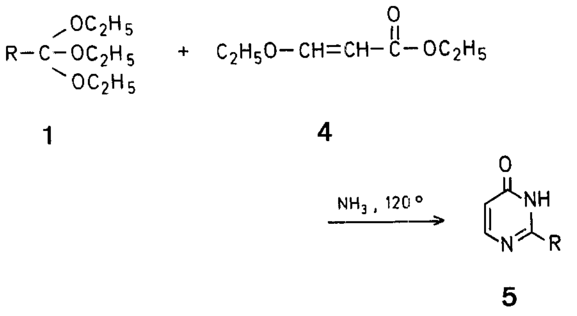
Orthoesters (**1**), which are commercially available at low cost, when allowed to react with β-ketoesters (**2**) and ammonia in refluxing ethanol, gave 2,6-disubstituted-4(3*H*)-pyrimidinones (**3**) in good yields.



Method A

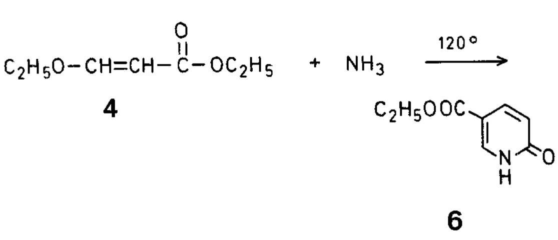
The products crystallized in relatively pure form upon concentration of the reaction mixtures. It is significant to note that triethyl orthoformate was not converted to 6-substituted-4(3*H*)-pyrimidiones (**3**, $R^1 = H$) under similar conditions.

2-Substituted-4(3*H*)-pyrimidinones (**5**) were obtained in good yields by reaction of orthoesters (**1**) with ethyl β-ethoxyacrylate[2] (**4**) and ammonia at 120°.



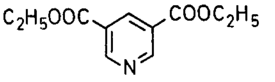
Method **B**

In the absence of orthoesters, **4** reacted with ammonia (mol ratio of **4**:$NH_3 = 2:1$ at 120° to give ethyl 2(1*H*)-pyridone-5-carboxylate (**6**) in 90% yield.



Method **C**

In the presence of excess ammonia, **4** reacted to give a mixture of **6** and diethyl pyridine-3,5-dicarboxylate (**7**) in yields of 32% and 28% respectively.



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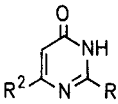
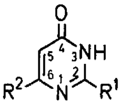
An extension of this reaction, using β-substituted analogs of **4**, might prove to be a useful synthetic approach to 4,6-disubstituted analogs of **6** and/or 2,4,6-trisubstituted analogs of **7**.

Table 1. Yield and Melting Point Data for 4(3*H*)-Pyrimidinones.



Compound	R^1	R^2	Yield (%)	Method	M.p.	Lit. m.p.	Ref.
5a	H	H	59	B	162–164°	163–165°	4
5b	CH_3	H	86	B	211–213°	213–214°	5
3a	CH_3	CH_3	58[3]	A	190–192°	192–193°	6
3b	CH_3	C_6H_5	55[3]	A	235–237°	238–240°	7
5c	C_2H_5	H	78	B	116–118°	118.5–120.5°	8
3c	C_2H_5	CH_3	50[3]	A	158–159°	160°	9
3d	C_2H_5	C_6H_5	98[3]	A	227–229°	238°	10

Table 2. ^{1}H-N.M.R. Data for 4(3*H*)-Pyrimidinones.



Compound	R^1	R^2	5-H	R^1	R^2	Solvent
5a	H	H	6.24 (d, 1H)	8.29 (s, 1H)	7.94 (d, 1H)	D_2O
5b	CH_3	H	6.39 (d, 1H)	2.42 (s, 3H)	7.95 (d, 1H)	D_2O
3a	CH_3	CH_3	6.22 (s, 1H)	2.49 (s, 3H)	2.32 (s, 3H)	$CDCl_3$
3b	CH_3	C_6H_5	6.88 (s, 1H)	2.88 (s, 3H)	7.77 (s, 5H)	$D_2O \cdot DCl$
5c	C_2H_5	H	6.37 (d, 1H)	1.21 (t, 3H) 2.68 (q, 2H)	7.95 (d, 1H)	D_2O
3c	C_2H_5	CH_3	6.35 (s, 1H)	1.17 (t, 3H) 2.68 (q, 2H)	2.28 (s, 3H)	D_2O
3d	C_2H_5	C_6H_5	6.82 (s, 1H)	1.48 (t, 3H) 3.15 (q, 2H)	7.72 (s, 5H)	$D_2O \cdot DCl$

2,6-Disubstituted-4(3H)-pyrimidinones (3); General Procedure:

A solution of orthoester (0.1 mol) and β-ketoester (0.05 mol) in 95% ethanol (15 ml) was added dropwise over a period of 5 h to a gently refluxing mixture of conc. ammonium hydroxide (3 ml) and 95% ethanol (6 ml) that had been saturated with ammonia. Heating at reflux was continued for 6 h after completion of the addition. During this time 0.5 ml portions of ethanol saturated with ammonia were added at 15 min intervals. This reaction mixture was evaporated to about one-third of its original volume, chilled, and the product[3] was collected by filtration. Recrystallization from acetone gave **3** in the yields indicated.

Ethyl β-Ethoxyacrylate (4)[4]:

Granulated zinc (500 g) was washed with dilute hydrochloric acid, then rinsed three times each with water, methanol, and acetone and then dried at 110° and 20 torr for 10 minutes. Dry benzene (125 ml) was added immediately to the zinc and the mixture was stirred vigorously and heated to reflux. A solution of ethyl bromoacetate (167 g) and ethyl orthoformate (300 ml, freshly distilled) in dry benzene (350 ml) was added dropwise over a period of 1 h while the mixture was maintained at a vigorous reflux. An additional 60 g of zinc (treated as above) was added and stirring and refluxing were continued for six hours. The mixture was cooled and poured into ether (1.0 l) and ice (500 g). Sufficient acetic acid was added at 0° to cause the light yellow precipitate to dissolve. The ether layer was washed with water and then with dilute sodium hydrogen carbonate, dried over anhydrous sodium sulfate, and the ether evaporated. The residue was vacuum distilled to give **4**; yield: 84 g (59%); b.p. 75–78°/6 torr (lit. 189 to 193°).

2-Substituted-4(3*H*)-pyrimidinones (5); General Procedure:

A mixture of ethyl β-ethoxyacrylate (**4**, 5.0 g, 0.035 mol) and orthoester (0.035 mol) in a 60 ml Parr tubular bomb was cooled in an isopropyl alcohol/dry ice bath and liquid ammonia (~2 ml) was added. The resulting mixture was heated at 120° for 12 hours. Evaporation of the volatile by-products gave a dark residue which was vacuum sublimed (R = H, CH_3), or recrystallized from petroleum either (R = C_2H_5), to give **5** in the yields indicated in Table 1.

Ethyl 2(1*H*)-pyridone-5-carboxylate (6):

To **4** (5.0 g) in a 60 ml Parr tubular bomb cooled in an isopropyl alcohol/dry ice bath was added liquid ammonia (~0.3 ml). The resulting mixture was heated at 120° for 12 h. The residue was sublimed and recrystallized from acetone to give **6**; yield: 2.6 g (90%); m.p. 145–146° (Lit. m.p. 149–151°).

$C_8H_9NO_3$	calc.	C 57.48	H 5.43	N 8.38
	found	57.37	5.36	8.28

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.36$ (t, 3H), 4.37 (t, 2H), 6.6 (d, 1H), 8.08 (d, d, 1H), 8.29 ppm (d, 1H).

Reaction of 4 With Excess Ammonia:

The reaction was carried out as described above, except that ~2.0 ml of liquid ammonia was used. Vacuum distillation of the product mixture gave **7**; yield: 1.0 g; b.p. 122–146°/0.9 torr; m.p. 45–47° (lit. m.p. 48–48.5°).

$C_{11}H_{13}NO_4$	C 59.18	H 5.87	N 6.28
	59.25	5.86	6.13

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.45$ (t, 6H), 4.52 (q, 4H), 8.56 (t, 1H), 9.08 ppm (d, 2H).

The residue from the vacuum distillation was sublimed and recrystallized to give **6**; yield: 1.3 g (32%) having the properties described above.

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[1] For some typical examples see: H. R. Snyder, H. M. Foster, *J. Amer. Chem. Soc.* **76**, 118 (1954); and T. Kato, H. Yamanaka, T. Shibata, *Yak. Zass.* **87**, 955 (1967).
For a comprehensive review see: D. J. Brown, "*The Pyrimidines*", in "*The Chemistry of Heterocyclic Compounds*", Volume 16, A. Weissberger, Ed., Interscience Publishers, New York, 1962.

[2] Prepared by a modification of the method reported by N. C. Deno, *J. Amer. Chem. Soc.* **69**, 2233 (1947).

[3] The crude yields were about 80%. N.M.R. analyses did not indicate the presence of any substantial amounts of impurities in the crude products.

[4] L. Bauer, B. A. Mikrut, G. E. Wright, C. L. Bell, *J. Heterocycl. Chem.* **2**, 477 (1965).

[5] S. Gabriel, *Ber. dtsch. chem. Ges.* **37**, 3688 (1904).

[6] E. von Meyer, *J. prakt. Chem.* [2], **27**, 152 (1883).

[7] G. Shaw, G. Sugowdz, *J. Chem. Soc.* **1964**, 665.

[8] J. P. Jonak, G. C. Hopkins, H. J. Minnemeger, H. Tieckelmann, *J. Org. Chem.* **35**, 2512 (1972).

[9] R. Wollner, *J. prakt. Chem.* [2], **29**, 131 (1884).

[10] A. Pinner, *Ber. dtsch. chem. Ges.* **22**, 1612 (1889).